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VOLUME 28 NUMBER 4

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OCTOBER 15, 1921

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

JUNE, 1921. NUMBER 6

The Incidence and Histopathology of Tuberculosis of the Tonsils Based on Eight Thousand Six Hundred Tonsillectomies. Carl Vernon Weller, Ann Arbor, Mich.

I. Liver Regeneration Following Chloroform Injury as Influenced by the Feeding of Casein or Gelatin. N. C. Davis and G. H. Whipple, M. D., San Francisco.

Studies in the Response of the Circulation to Low Oxygen Tension. IV. A Sphygmographic Study of the Pulse During the Rebreather Test. N. C. Gilbert, M.D., Chicago, and Charles W. Greene, Ph.D., Columbia, Mo.

The Use of a High Fat Diet in the Treatment of Diabetes Mellitus. Second Paper: Blood Sugar. L. H. Newburgh, M.D., and Phil. L. Marsh, M.D., Ann Arbor, Mich.

Fatal Chronic Nephritis in a Fourteen Year Old Girl with Only One Kidney and a History of Scarlet Fever. O. H. Perry Pepper, M.D., and Baldwin Lucke, M.D., Philadelphia.

New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man. C. W. McClure, M.D., A. S. Wetmore and Lawrence Reynolds, M.D., Boston.

Dermatitis and Allied Reactions Following the Arsenical Treatment of Syphilis. Joseph Earle Moore, M.D., and Albert Keidel, M.D., Baltimore.

The Total Nonprotein Nitrogen Constituents of the Blood in Arterial Hypertension. J. Lisle Williams, M.D., Chicago.

Book Review.

Index to Volume 27.

JULY, 1921. NUMBER 1

Renal Irritation in Man from High Protein Diet. Theodore L. Squier, M.D., and L. H. Newburgh, M.D., Ann Arbor, Mich.

II. The Effect of Cyanids and of Organic Oxidizing Agents on the Liver Injury Caused by Chloroform. N. C. Davis, M.D., San Francisco.

The Intravenous Use of Foreign Protein in the Treatment of Chronic Cases of Arthritis with Special Reference to the Use of Secondary Proteose. R. Garfield Snyder, M.D., and Maximilian A. Ramirez, M.D., New York.

On the Etiology of an Outbreak of Infectious Diarrhea. Harry Weiss, Boston.

Renal Glycosuria. Phil L. Marsh, M.D., Ann Arbor, Mich.

The Right Ventricle in Pulmonary Tuberculosis. Ernest P. Boas, M.D., and Hubert Mann, M.D., New York.

Frequent Causes and the Treatment of Seasonal Hay-Fever. I. Chandler Walker, M.D., Boston.

Some Urinary Changes in Normal Individuals on the Pellagra Producing Experimental Diet. M. X. Sullivan, Spartanburg, S. C.

Book Review.

AUGUST, 1921. NUMBER 2

Objects and Methods of Diet Adjustment in Diabetes. R. T. Woodyatt, M.D., Chicago.

Acute Yellow Atrophy of the Liver. Max Kahn, M.D., Ph.D., and Joseph Barsky, M.D., New York.

Food Allergy as a Cause of Abdominal Pain. William W. Duke, M.D., Kansas City, Mo.

Phenols in the Urine in Pellagra. M. X. Sullivan and Paul R. Dawson, Spartanburg, S. C.

The Basal Metabolism and the Specific Dynamic Action of Protein in Liver Disease. Joseph C. Aub, M.D., and James H. Means, M.D., Boston.

The Diagnosis of Eventration of the Diaphragm with a Report of a Case of Aplasia of the Right Lung and Right Half of the Diaphragm, Associated with Congenital Dextrocardia. Horace Marshall Korns, M.D., Cleveland.

The Bigeminal Pulse in Atroventricular Rhythm. Paul D. White, M.D., Boston.

The Synthesis and Elimination of Hippuric Acid in Nephritis: A New Renal Function Test. Preliminary Paper. F. B. Kingsbury, Ph.D., and W. W. Swanson, B.S., Minneapolis.

Book Review.

SEPTEMBER, 1921. NUMBER 3

Epitheliomata of Thymic Origin. Douglas Symmers, M.D., and B. M. Vance, M.D., New York.

Betelnut Chewing and Its Effects, Including Cancer of the Mouth. Aller G. Ellis, M.D., Bangkok, Siam.

On the Causes of the Variations in the Sedimentation of the Corpuscles and the Formation of the Crusta Phlogistica ("Size," "Buffy Coat") on the Blood: a Preliminary Communication. H. C. Gram, Copenhagen, Denmark.

Carotinemia: Report of a Case in an Adult. George Douglas Head, M.D., and Reuben A. Johnson, M.D., Minneapolis.

Focal Infection and Elective Localization in the Etiology of Myositis. Edward C. Rosenow, M.D., and Winifred Ashby, Ph.D., Rochester, Minn.

Observations on the Relation of Urea to Uremia. Louis Leiter, Chicago.

Metabolic Studies on a Case of Diabetes Insipidus. I. M. Rabinowitch, M.D., Montreal, Canada.

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Archives of Internal Medicine

VOL. 28 OCTOBER, 1921 No. 4

STUDIES IN OXYGEN THERAPY WITH DETERMINATIONS OF THE BLOOD GASES

I. IN CARDIAC INSUFFICIENCY AND RELATED CONDITIONS *

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AND
MARGARET N. WOODWELL, A.B.
BOSTON

TABLE OF CONTENTS

1. Harmful effects produced by an insufficient oxygen supply.
2. Evidence that an insufficient oxygen supply exists in clinical disease.
3. Desirability of raising oxygen content of blood to normal level.
4. Methods of administration in recent war.
5. Method developed in this investigation.
6. Illustrative cases of cardiac disease, bronchitis, edema of the lungs. (Pneumonia, edema of the lungs, empyema and respiratory paralysis considered in Papers II and III.)
7. Increase in oxygen content of blood following oxygen inhalation.
8. Clinical improvement that occurs in acute anoxemia, following oxygen inhalation.

INTRODUCTION

The purpose of this investigation was primarily to determine what conditions of oxygen want could be relieved by the therapeutic inhalation of oxygen. The degree of anoxemia was determined by the oxygen saturation of the arterial and venous blood. The effect of oxygen administration was thus quantitatively measured by comparison of values before and after treatment. The correlation of the oxygen changes in the blood with the objective and subjective changes in the patient gave the opportunity of determining whether clinical improvement resulted from oxygen therapy. There were considered in all

* From the Medical Service of the Massachusetts General Hospital. This paper is No. 15 of a series of studies of the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

* The expense of this work was in part defrayed by a grant from the Proctor Fund of Harvard University for the study of chronic diseases.

two normal subjects, seven patients with cardiac insufficiency, twelve patients with pneumonia, and two patients with lethargic encephalitis. As the cases had to be studied individually, it became advisable for the sake of clearness to divide them into a cardiac group (Paper I), a pneumonia group (Paper II), and a group characterized by a type of shallow breathing in lethargic encephalitis (Paper III). An outcome of the work has been the development of an effective and practicable method of providing oxygen.

HISTORICAL

A few facts will be reviewed from the literature with the purpose of presenting a theoretical basis for the giving of oxygen. Barcroft [1] has shown from his own work and the work of others that any activity of the body organs involves a call for oxygen. Exact measurements have been made for the heart, kidney, muscle and the secreting glands which show that increased work is done only with a proportional increase in oxygen consumption. Stoppage of the oxygen supply brings the perfused heart to a standstill, causes a cessation in the flow of urine, decreases the conduction of nerve tissue, produces muscular fatigue, and at last immobility. Bayliss,[2] after reviewing the oxygen consumption of resting and active tissues, concluded that "an organ may suffer from oxygen want, even when the venous blood coming from it still contains oxygen, so that the oxygen passes the cells unused. It is probable that for proper functional work, oxygen must be supplied not only in certain amount, but at a tension not far below that in which it is present in the atmosphere and in the arterial blood."

The direct effects of anoxemia, as recently summarized by Haldane,[3] have been obtained by observations at high altitudes, by laboratory experiments in which a lowered partial pressure of oxygen is breathed in chambers, and by the consequences of carbon monoxid poisoning, where the oxygen carrying power of hemoglobin is partly destroyed. One of the first symptoms of oxygen want, when gradually produced, is periodic breathing. At high altitudes, this is practically a normal phenomenon. The further symptoms include distinct impairment of mental faculties, often showing itself in manifestations similar to alcoholic intoxication. The powers of judgment, self control, and memory are definitely impaired. After some hours, there are nausea and headache, and often vomiting and diarrhea. If the exposure has been very long, though slight, these symptoms may still persist, even if meanwhile their cause has been removed. When lack of

1. Barcroft, J.: The Respiratory Function of the Blood, 1914, p. 105.
2. Bayliss, W. M.: Principles of General Physiology, 1918, p. 343.
3. Haldane, J. S.: Recent Developments in the Therapeutical Use of Oxygen. Contributions to Medical and Biological Research Dedicated to Sir William Osler **1**:550, 1919.

oxygen has been more serious, the pulse becomes rapid and feeble, periodic respiration gives place to rapid, shallow respiration, consciousness becomes greatly impaired or lost, and progressive damage is done to central nervous system, heart and other organs. The evidence is conclusive, Haldane believes, that these characteristic effects are due solely and simply to lack of oxygen.

The existence of cyanosis is prima facie evidence of lack of oxygen in clinical disease. Abnormal oxygen unsaturation of the venous blood in cardiac disease was found by Means and Newburgh.[4] Lundsgaard[5] later established the normal values of oxygen saturation of venous blood, and showed in various types of cardiac insufficiency abnormal oxygen unsaturation. The introduction of the arterial puncture by Hürter,[6] and its successful development by Stadie,[7] made the arterial blood of human beings accessible for study for the first time. Diminished arterial oxygen saturation was then shown to occur in pneumonia by Stadie,[7] and in cardiac insufficiency by Harrop.[8] In these investigations, the close relationship between cyanosis and the amount of reduced hemoglobin in the blood was established. The oxygen saturation of normal resting individuals may be taken as 95 to 98 per cent. for the arterial blood, and 65 to 75 per cent. for the venous blood.

Recently, Barcroft[9] lived for six days in an atmosphere in which the partial pressure of oxygen fell to 84 mm. On the last day, the oxygen saturation of his arterial blood was 88 per cent., and after the performance of work 83.8 per cent. He lay in the chamber racked with headache, with occasional vomiting, and at times able to see clearly only as an effort of concentration. He became faint on exertion. His pulse, normally 56, had risen to 86. These effects were apparently due purely to oxygen want. The degree of anoxemia that produced them has frequently been found in pneumonia and heart disease by the investigators mentioned above. In many instances, the saturation of the arterial blood falls to far lower levels. It would, therefore, seem likely that lack of oxygen in the degree often found in disease would produce bodily discomfort, disturbances in function and damage to living structure.

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4. Means, J. H., and Newburgh, L. H.: Studies on the Blood Flow by the Method of Krogh and Lindhard. Tr. Assn. Am. Phys., 1915, p. 51.

5. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, J. Exper. M. **27**:179, 1918.

6. Hürter: Deutsch. Arch. f. klin. Med. **108**:1, 1912.

7. Stadie, W. C.: The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, J. Exper. M. **30**:215, 1919.

8. Harrop, G. A.: The Oxygen and Carbon Dioxid Content of Arterial and Venous Blood in Normal Individuals and in Patients with Anemia and Heart Disease, J. Exper. M. **30**:241, 1919.

9. Barcroft, J.; Cook, A.; Hartridge, H.; Parsons, T. R., and Parsons, W.: Flow of Oxygen Through the Pulmonary Epithelium, J. Physiol. **53**:450, 1920.

As a further consideration, there sometimes is an increased metabolic demand for oxygen in the diseases in which anoxemia is itself conspicious. In cardiac insufficiency, an increased basal metabolism has been demonstrated.[10] Fever causes an increased metabolism which has been proved to be proportional to the increase in fever.[11] It is of interest in this connection that the performance of physical exercise in normal men can be done easier, with less dyspnea and less fatigue, when oxygen is added to the inspired air.[12] This has been shown to be especially true of unfit men.[13] Since oxygen helps the accomplishment of physical work in normal men, it might be expected to aid in the performance of the increased work in cardiac insufficiency and pneumonia. The above favorable results in the absence of anoxemia must depend on the increase of oxygen in physical solution.

We may refer briefly to certain recent methods of giving oxygen. The frequent occurrence of gas poisoning during the war led to a hurried demand for oxygen therapy. The condition produced by the irritant gases was an acute primary edema of the lungs characterized clinically by air-hunger and an extreme degree of cyanosis. Haldane[14] devised an apparatus by which measured quantities of oxygen could be added to the inspired air, thus greatly increasing the available diffusion pressure through the alveolar wall. The essentials were an oxygen tank, a reducing valve, and a face mask. The mask was connected with a collecting bag which received oxygen from the tank, and with the outside air, from which the patient breathed. Oxygen was added to the inspired air in amounts of from one to four liters per minute. This was largely used in the acute cases with generally good results. Douglas[15] found it very effective. Less effective was the nasal tube method, and still less effective and even more wasteful was the tube and funnel method. In the funnel method, Meltzer[16] has calculated that the atmospheric air is not richer by more than 2 per cent., if by so much. Cummins[17] found it difficult to make the

10. Peabody, F. W.; Meyer, A. L., and Du Bois, E. F.: Basal Metabolism of Patients with Cardiac and Renal Disease, Arch. Int. Med. **17**:980 (July) 1917.

11. Coleman, W., and Du Bois, E. F.: The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, Arch. Int. Med. **14**:168, 1914. Also Du Bois, E. F.: Respiration Calorimeter in Clinical Medicine, Am. J. M. Sc. **178**:792, 1916.

12. Hill, L., and Flack, M.: Influence of Oxygen on Athletes, J. Physiol. **38**:12, 1909.

13. Briggs, H.: Fitness and Breathing, J. Physiol. **54**:292, 1920.

14. Haldane, J. S.: Therapeutic Administration of Oxygen, Brit. M. J. **1**:181, 1917.

15. Douglas, C. G.: Discussion on Therapeutic Uses of Oxygen, Proc. Roy. Soc. Med. (Sec. Therap. & Pharmacol.) **13**:59, 1920.

16. Meltzer, S. J.: Therapeutic Value of Oral Rhythmic Insufflation of Oxygen, J. A. M. A. **69**:1150 (Oct. 6) 1917.

17. Cummins: Discussion on Therapeutic Uses of Oxygen, Proc. Roy. Soc. Med. (Sec. Therap. & Pharmacol.) **13**:59, 1920.

men stand the mask of the Haldane apparatus. Ryle [18] used the nasal catheter, introduced by Stokes, with fairly good results. Masks were improvised at his station, but were not tolerated by the men. Hamil [19] considered the nasal tube satisfactory, but wasteful, and also found the mask badly tolerated, especially in warm climates. Hoover [20] said the gassed men begged to be relieved of the mask and preferred to have the oxygen conducted by a soft rubber tube in their nostrils, though by the latter method he did not see a single case in which the cyanosis was diminished.

The chronic cases of gas poisoning were treated in oxygen chambers at home, with striking evidences of improvement. The group described by Barcroft, Hunt and Dufton [21] exhibited disorder action of the heart, nocturnal dyspnea, high red blood cell counts, low percentages of carbon dioxid in the alveolar air, acidosis and kindred conditions. The patients were kept in a chamber of 50 per cent. oxygen for sixteen out of the twenty-four hours for five days. Almost all of them showed a disappearance of symptoms. Shufflebotham and Lowry [22] treated cases of chronic gas poisoning in oxygen chambers with equally marked improvement. They also treated one case of lobar pneumonia and one case of bronchopneumonia with promising results. Meakins [23] treated a case of chronic gas poisoning with the Haldane apparatus, giving oxygen for three one-hour periods daily for seven days. The patient became cured of all symptoms. The arterial oxygen saturation was normal at the beginning, and increased by oxygen. He also reported three cases of pneumonia and five cases of asthma, emphysema and chronic bronchitis, in which the arterial saturation was elevated by oxygen administration, and in whom marked improvement resulted. No determinations of the venous blood were done, nor were any cases of cardiac insufficiency studied. For patients who will not, or cannot, put up with a mask, Hill [24] constructed a simple oxygen bed tent, which encloses the upper part of the patient when in bed. Arrangements are made for inlet and outlet of air and oxygen, for absorption

18. Ryle: Ibid.

19. Hamil: Ibid.

20. Hoover, C. F.: Oxygen Therapy. J. A. M. A. **71**:880 (Sept. 14) 1918.

21. Barcroft, J.; Hunt, G. H., and Dufton, D.: The Treatment of Chronic Cases of Gas Poisoning by Continuous Oxygen Administration in Chambers. Quart. J. M. **13**:179, 1920.

22. Shufflebotham, F., and Lowry, G. H.: Discussion on Therapeutic Uses of Oxygen, Proc. Roy. Soc. Med. **13**:59, 1920.

23. Meakins, J. C.: Observations on the Gases in Human Arterial Blood in Certain Pathological Pulmonary Conditions, and Their Treatment with Oxygen. J. Path. & Bact. **24**:87, 1921.

24. Hill, L.: A Simple Oxygen Bed Tent and Its Use in a Case of Edema and Chronic Ulcer of the Leg. J. Physiol. **50**: (May 24) 1921; Proc. Physiol. Soc., p. 20.

of carbon dioxid, and for circulation of the air. A window of non-inflammable celluloid is placed in front of the patient. A soldier was treated who had had his femoral artery tied, and suffered from coldness, blueness, edema and chronic ulcers of the leg. In forty-eight hours, the oxygen made the extremity warm and of good color, removed the edema, cleaned up the ulcers, and started the healing in a remarkable way.

METHODS

The methods used in this investigation for giving oxygen have represented a gradual development in the apparatus used and in the duration of treatment. With the purpose first of determining to what extent and for what length of time oxygen could be increased in the blood, short periods of administration were given. Later, prolonged and repeated administration of oxygen was given with more of a therapeutic object. The first apparatus consisted simply of a face mask, connected through a soda-lime canister with a rebreathing bag, in turn connected with an oxygen tank. In this way, the patient rebreathed pure oxygen, the carbon dioxid being absorbed by soda-lime. This was soon modified by the insertion in the mask of a small inlet and outlet valve connected with the outside air. This provided the patient with about an 80 per cent. oxygen mixture. All the connections were made one inch wide so that no resistance was felt on respiration. This was efficient, easily put together, and economical in the expenditure of oxygen. Its disadvantage was the use of the mask. There were a few patients who took it without objection and in comparative comfort. The greater number could not bear the suffocating feeling which they said it produced, and struggled against it. Especially when the patient was suffering with urgent dyspnea, or in warm weather, the mask was poorly tolerated. Later, when the Haldane apparatus was used, the same difficulty was experienced. When the patient was in coma the Haldane apparatus was very useful, for it was convenient to adjust the inlet of oxygen to the rate desired and leave it on for long periods. For the patients who would not submit to oxygen administration by a mask of any sort, a soft rubber mouthpiece such as is used in the Benedict Respiration apparatus was tried in its place with the rest of the rebreathing outfit unchanged. This proved to be very satisfactory. It fits easily into the mouth, its opening is wide enough for all respiration to take place through it, and its flanged margins support it and prevent leaking. When held or attached so that no pressure is brought to bear on the patient's mouth, it is comfortable, and causes nothing in the way of suffocation. When the nose is held, pure oxygen is rebreathed. This diminishes comfort, and was found to be unnecessary and undesirable, since patients get a rich oxygen mixture even when breathing through nose and mouth. The patient is asked

to breathe through his mouth, and usually adapts himself easily to the mouthpiece, breathing from four to seven parts oxygen through his mouth, and from three to six parts air through his nose. In the pneumonia patient, breathing takes place through mouth and nose even more naturally, and a mixture of about 50 per cent. oxygen is usually inhaled. By watching the excursion of the rebreathing bag, the percentage of oxygen being breathed can be roughly estimated. The nose is held closed for a few inspirations, making all respiration take place through the mouth. When the nose is released, the diminution in the excursion of the bag indicates the proportion of breathing through the nose. This is, of course, only approximate, but there is no need for knowing the precise composition of the mixture. (Where this is desired, a Douglas bag can previously be filled with a known mixture of oxygen, and attached in place of the tank.) There seem to be two important considerations in giving oxygen: one, that an effective oxygen mixture be used; two, that pure oxygen should not be given for long periods. Lorrain Smith [25] was able to produce pneumonia in animals by having them live in atmospheres of pure oxygen for several days. Karsner [26] also produced pneumonia in rabbits by having them breathe from 80 to 90 per cent. oxygen in chambers for two or more days, but was able to demonstrate no noteworthy changes in other organs. Mixtures under 70 per cent. oxygen can be breathed indefinitely without harmful effect.[27] That no increase in the vital process occurs during the inhalation of pure oxygen was first demonstrated by Lavoisier and Seguin [28] in 1789, and after a century of dispute was finally carefully confirmed by Benedict and Higgins.[29]

There are patients who will for a while inhale through the mouth and exhale through the nose or inhale through the nose and exhale through the mouth, in the first case not rebreathing and consequently wasting the oxygen, and in the second place distending the rebreathing bag. This is usually remedied by instruction. There are, of course, patients in active delirium who will not put up with mask or mouthpiece. As a rule, however, the patient takes the mouthpiece well, and breathes a satisfactory mixture. No matter how ill, it involves no actual burden; patients who struggled against the mask frequently took the mouthpiece quietly and even dozed off during the administration. (See illustration for arrangement of apparatus).

25. Smith, J. L.: The Pathological Effects Due to Increase of Oxygen Tension in the Air Breathed, J. Physiol. **24**:19, 1899.

26. Karsner, H. T.: The Pathological Effects of Atmospheres Rich in Oxygen, J. Exper. M. **23**:149, 1916.

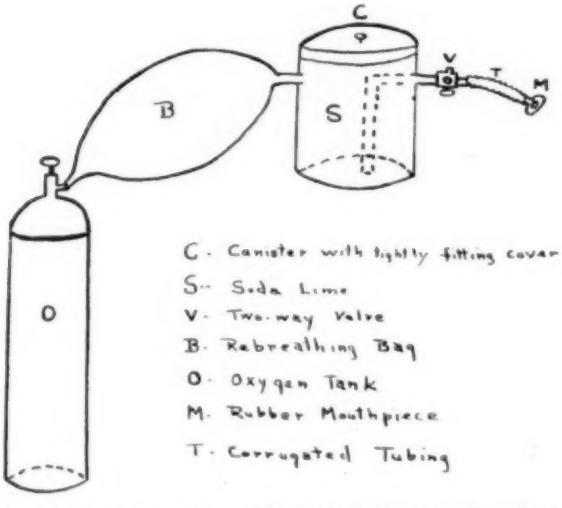
27. Flack, M., and Hill, L.: Textbook of Physiology, 1919, p. 303.

28. Lavoisier and Seguin: Mem. de l'Acad. des Sc., 1789, p. 185.

29. Benedict, F. G., and Higgins, H. L.: Effects on Men at rest of Breathing Oxygen-Rich Gas Mixtures, Am. J. Physiol. **28**:1, 1916.

The apparatus is easily put together and carried about, and is not wasteful in its consumption of oxygen. (The duration and efficiency of the soda-lime can be tested by running the air in the rebreathing bag through a barium hydrate solution.)

The gas analysis, except for the instances mentioned below, was done by Van Slyke and Stadie's [30] method of determining oxygen and carbon dioxid on the same sample of blood. A modified Van Slyke vacuum apparatus is used, in which the pipet is twice the length and one-half the diameter of the original one, and calibrated to 0.01 c.c. The Van Slyke [31] method of determining oxygen alone (with the recent correc-



Apparatus for giving oxygen. The patient breathes through the rubber mouthpiece M through the can of soda-lime C into a rebreathing bag B. The carbon dioxid exhaled is removed by the soda-lime, and oxygen is admitted from the tank O at a sufficient rate to keep B inflated. In this way the patient rebreathes pure oxygen from the apparatus, but since his nose is left open he dilutes this with a certain proportion of atmospheric air. In practice this results in the inhalation of from 40 to 60 per cent. oxygen.

tions for dissolved gases) was used in Case 4, the analyses in Case 3 that were done Oct. 16 and Oct. 20, 1921, and the analyses in Case 2 that were done Oct. 6, 1921. The arterial and venous blood was drawn wihout stasis under oil after the method described by Stadie.[7] The analyses were done in duplicate, in most cases directly after the blood was taken. When the blood was allowed to stand from one to three

30. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem., To be published.
31. Van Slyke, D. D.: Gasometric Determination of the Oxygen and Hemoglobin of Blood, J. Biol. Chem., **33**:127, 1918.

hours it was kept on ice. Lundsgaard found that blood under oil on ice suffered no change in oxygen content in twenty-four hours. Control determinations done by ourselves at these varying intervals showed no significant change in gas content.

PRESENTATION OF DATA

It will help in the consideration of our cases if the several types of anoxemia are borne in mind. According to the classification of Barcroft,[32] they are as follows:

1. *Anoxic Type.*—The pressure of the arterial blood is too low. The arterial oxygen saturation of the hemoglobin is below normal, i. e., below 95 per cent. Mountain sickness is an example in which the diminished partial pressure of oxygen in the blood is due to the diminished partial pressure of oxygen in the atmosphere. In edema of the lungs, the oxygen at prevailing pressures cannot diffuse properly through the diseased alveolar wall, and some unrespired blood is passed into the aortic stream, lowering the arterial saturation.

2. *Stagnant Type.*—The quantity of oxygen which reaches the tissues in unit of time is less than normal because of a slowed blood flow. More oxygen is used up in the capillaries and the venous blood has a lowered oxygen saturation, below 65 per cent.

3. *Anemic Type.*—A diminished amount of available hemoglobin is present, which involves a lessened capacity to carry oxygen. This condition may be due to an actual diminution in the number of red blood cells, or the hemoglobin may be converted into methemoblogin, or monopolized by carbon monoxid so that its oxygen carrying function is destroyed.

The anoxic type is primarily due to pulmonary causes, i. e., faulty oxygenation of blood as it flows through the lungs. The stagnant type is primarily due to cardiac causes, i. e., decreased rate of blood through the systemic capillaries. In cardiac insufficiency, the two frequently occur together, the stagnant type because of poor heart action, the anoxic type because of the secondary conditions of pulmonary congestion and edema.

PROTOCOL OF EXPERIMENTS

The individual cases follow, the first two being normal controls:

CASE 1 (Table 1).—Normal. White female, research worker; age, 23 years.

EXPERIMENT.—Nov. 18, 1920. Subject in recumbent position, three hours after breakfast. Pure oxygen was given through a mask for one-half hour. There was no change in color of skin or mucous membranes. No change subjectively. Venous saturation before oxygen 67.7 per cent.; after, 69.1 per

32. Barcroft, J.: Anoxemia, Lancet **1**:487, 1920.

cent.; venous carbon dioxid content before, 51.3 volume per cent.; after, 53 volume per cent. Pulse: 66 before, 60 after. Respiratory rate: 14 before, 16 after. Blood pressure: 140/80 before, 135/85 after. Vital capacity: 3,564 c.c. before, 3,424 c.c. after. Electrocardiogram showed normal rhythm before, and no change during or after oxygen.

CASE 2 (Table 1).—Normal. White male, physician; age, 26 years.

EXPERIMENT.—Oct. 6, 1920. Subject in recumbent position, forty-five minutes after lunch. Pure oxygen administered through a mask for one-half hour. Arterial saturation before, 96.6 per cent.; after, 99.6 per cent.; venous saturation 71.3 per cent. before. Venous blood at end of administration was taken after wrist had been bandaged tightly at site of artery puncture, and hence blood was under stasis when drawn. The saturation even under these conditions was 72.8 per cent.

EXPERIMENT 2.—Dec. 15, 1920. Subject in recumbent position, four and one-half hours after breakfast. Pure oxygen given through mask for one-half hour. Pulse before, 76; after, 68. Respiration before, 19; after, 21. There seemed to be deeper breathing during oxygen. Venous oxygen saturation: 73.5 per cent. before, 83 per cent. after. Venous carbon dioxid content: 52.4 volume per cent. before, 50.2 volume per cent. after.

In a normal man, the inhalation of oxygen for one-half hour increased definitely the oxygen content and saturation of arterial and venous blood. In a second individual, the inhalation of oxygen for the same period increased the oxygen content and saturation of venous blood to a very slight extent. The carbon dioxid content of venous blood was not markedly or consistently altered, although slight changes occurred in each experiment. These may have been produced by a change in breathing incident to the mask. Subjectively, there were no effects. Objectively, the slowing of the pulse was the only other definite finding. The blood pressure, vital capacity, rate of respiration, and electrocardiogram showed no significant changes.

REPORT OF CASES

CASE 3 (Table 2).—T. M., white, male, coachman; age, 57 years.

Diagnosis.—Cardiac insufficiency, chronic myocarditis, partial heart block, right bundle branch block.

History.—Rheumatic fever when young, without cardiac symptoms. Ten years alcoholic history. Fifteen months before this admission, patient first noticed dyspnea and swelling of the legs. Since then he has never been well, and for the six weeks before entry he has suffered from dyspnea, orthopnea and swelling of the legs and abdomen.

Physical Examination.—Oct. 15, 1920. Orthopnea and periodic respiration. Slight cyanosis of lips and mucous membranes. Moderate distention of neck veins. Heart much enlarged, apex in sixth space in anterior axillary line. Sounds regular, rapid, of poor quality. Systolic murmur over entire precordium. Pulse full, rate 90. Artery wall thickened. Blood pressure, 158/105. Dulness, diminished breath sounds, and moist râles at both bases. Shifting dulness in abdomen. Marked edema of legs. Irrational most of the time. Temperature normal. Urine: Specific gravity, from 1.022 to 1.030; slight trace of albumin. Blood Wassermann negative. Enlarged heart with widened arch on roentgenogram. Electrocardiogram showed delayed conduction and right bundle branch block. Nonprotein nitrogen 45.6 mg. per 100 c.c.

Course and Treatment.—Confined to bed; fluids restricted to 1,500 c.c.: digipuratim, 6 grains daily from Nov. 15 to 20, 1920.

On the night of admission, 400 c.c. of blood was removed, with a little relief.

Oct. 16, 1920: Condition same as on admission. At 10 a. m., oxygen saturation of the arterial blood was 87.5 per cent.,[33] the venous saturation 53.2 per cent. At 2:30 p. m., the venous saturation was 41.6 per cent. The only change was that he was more irrational in the afternoon. Pure oxygen was given through a mask uninterruptedly for one-half hour. At the end, the arterial saturation was 99.5 per cent., the venous saturation, 68.4 per cent. Fifteen minutes after the administration, the venous saturation was 67.4 per cent. The patient took the mask without complaint, and said he felt more comfortable after the inhalation. Periodic respiration was present before oxygen. After four minutes breathing became regular, of moderate depth, rate 30 per minute. One minute after removal of mask periodic respiration recurred. Cyanosis of lips disappeared and the ears became pink during the inhalation. Pulse: 90 before, 84 immediately after, 84 fifteen minutes after oxygen.

October 17: No cyanosis evident. Periodic respiration. Pulse 60.

October 19: Slight cyanosis of lips. Periodic respiration. Pulse 64.

October 20: Face a grayish dusky color, lips slightly cyanotic. Periodic respiration with long periods of apnea. Distention of neck veins, congestion in lungs, and edema of extremities were undiminished. Pulse from 40 to 50. Digitalis was stopped, 30 grains of digipuratim having been administered since admission. Oxygen was given through a mask for one-half hour. Arterial saturation before oxygen 83.5 per cent.; one and one-half hours after, 89.9 per cent. Venous saturation before, 53.7 per cent.; at the end of fifteen minutes oxygen, 71.6 per cent.; at the end of thirty minutes oxygen, 72.4 per cent.; one and one-half hours after the inhalation, 72.4 per cent. During the administration, his face noticeably pinkened, and dilated capillaries and venules stood out a bright red. After one minute's oxygen, the periodic respiration was changed to regular breathing, rate 32, finally slowing to 25. Five minutes after the administration, it was still regular, rate 26. Fifteen minutes later, Cheyne-Stokes respiration had recurred, with, however, short periods of apnea, in contrast to the long apneic periods present before oxygen. The pulse exhibited striking variations. At the start it was regular, rate 48 (digitalis effect). During the inhalation it became very irregular, rate rising to 88, until the end of the administration, when it again became regular, rate 68. Five minutes later, it was 48 and regular.

October 21: Patient was much quieter, more comfortable and slept better. Cheyne-Stokes respiration continued most of the time with short periods of apnea, rate 26. No cyanosis. Dilated venules and capillaries on face remained pink. Pulse from 50 to 60. Venous saturation 78.1 per cent. Venous carbon dioxid content 61.4 volume per cent.

October 23: No cyanosis, but face was pale. Signs of congestion in lungs less marked. Edema of legs a little diminished.

October 25: General condition unchanged. Cheyne-Stokes breathing present. Arterial saturation 96.6 per cent., venous saturation 77.4 per cent. Arterial carbon dioxid content, 56.2 volume per cent.; venous carbon dioxid content, 61 volume per cent. Oxygen was given for one-half hour, a valve effect in the mask being utilized to provide about 70 or 80 per cent. mixture. The mask was first connected with the room air. In one minute, periodic respiration was replaced by regular breathing, rate 33. Air was breathed for six minutes, and respiration continued regular, rate from 33 to 36 per minute.

33. The attempt was made to draw the arterial blood equally during apnea and dyspnea, but this could only be crudely approximated. That the phases of periodic respiration make an important difference in oxygen content is shown by subsequent determinations.

Oxygen was then given, and the breathing continued at about the same rate. His color previous to oxygen was pale, without cyanosis. After oxygen, his nose, cheeks, lips and ears were pink, and the dilated capillaries and venules became prominent and red. The pulse again showed interesting variations. Prior to the giving of oxygen, the rate varied with the phase of respiration, in dyspnea 48 per minute, in apnea 84 per minute. (Duration of apnea fifteen seconds.) During the inhalation the pulse rate quickened, and became very irregular, the irregularity being felt at the wrist as dropped beats, rate 88. Five minutes after oxygen, the pulse rate was 73, without dropped beats but varying slightly with the Cheyne-Stokes respiration, which had returned at this time. Shorter periods of apnea, however, were present, and the pulse variations were likewise smaller than before oxygen. At the end of the administration, the patient was asked to lie flat to see whether orthopnea persisted in the presence of a plentiful oxygen supply. He complained of immediate discomfort, and was allowed up. Patient was not clear mentally, and this response may have been a habit sensation rather than actual discomfort. The arterial saturation, taken forty minutes after the treatment, was 97.7 per cent., the arterial carbon dioxid content 59.2 volume per cent. The vital capacity immediately before oxygen was 1,194 c.c.; immediately after, 1,166 c.c.; two hours later, 1,166 c.c.

October 29: Clinical condition little changed. For past four days he has been allowed up in chair part of the day in attempt to restore clear mentality. Vital capacity 1,530 c.c.

October 31: Got up at night, walked about, fought efforts to replace him.

November 1: Temperature 101.5 F. Patient developed an acute bronchitis. Face had a dull grayish appearance; there was moderate cyanosis of lips and chin, and slight cyanosis of ears. Frequent productive cough present. He was more irrational. Cheyne-Stokes respiration continued. Pulse 100 in apnea; 80 in dyspnea. Vital capacity 942 c.c. Lungs showed scattered sibilant and sonorous râles over both chests, with dulness, diminished breathing and moist râles at right base. Mask was connected to room air to test effect on breathing. No change occurred, Cheyne-Stokes breathing persisting for entire fifteen minutes of experiment. An attempt was made to get arterial blood separately in apnea and dyspnea but the syringe filled too slowly to get unmixed samples. The arterial saturation obtained in apnea was 85.2 per cent., in dyspnea 87 per cent.; the arterial carbon dioxid content in apnea was 56.7 volume per cent., in dyspnea 59.3 volume per cent.

November 3: Temperature fell to 99.5 F. Periodic respiration present with periods of apnea lasting from 15 to 20 seconds. Samples of arterial blood were obtained with less overlapping today. The arterial saturation in apnea was 78.3 per cent., in dyspnea 85.2 per cent. The arterial carbon dioxid content in apnea was 61.4 volume per cent., in dyspnea 62 volume per cent. Oxygen was given through a mask for one-half hour. At the start, the mask was connected with the room air, and in one minute the respiration became regular. When the mask was removed, Cheyne-Stokes breathing immediately recurred. The mask was then adjusted connected with oxygen, and in one minute the breathing again became regular, rate 34. At the end of the administration the cyanosis had completely disappeared. The capillaries and dilated venules on the face stood out bright red. The venous saturation was 94.5 per cent. The arterial saturation was not tested, but was obviously raised to the normal or above. Before oxygen the pulse was 96 in apnea and 56 in dyspnea. The electrocardiogram showed auriculoventricular block and right bundle branch block; in the dyspneic phase, sino-auricular slowing and increase of auriculoventricular block; in the apneic phase, increase of sino-auricular rate without dropped beats. During oxygen administration, with regular breathing, the pulse was regular, rate 84 to 92. The electrocardiogram confirmed the regularity, showed an absence of the marked auriculoventricular block, a decrease in the height of the R wave and less notching of the R complex.

Ten minutes after the administration ,periodic respiration began again, though with much shorter periods of apnea. Pulse 88 in apnea, 74 in dyspnea. The electrocardiogram preserved the characteristics it had during oxygen administration. One-half hour later, pulse and electrocardiographic findings were the same. Two hours later, pulse and respiratory variations were the same as after oxygen. Immediately after oxygen, patient noticed no subjective relief; two hours later he said he breathed more easily. No cyanosis was evident. Blood pressure before and after inhalation 150/110. Vital capacity before, 942 c.c.; after, 858 c.c.

November 4: No cyanosis evident. On the following morning he was removed to a chronic cardiac convalescent hospital. He died Nov. 8, 1920.

In this case, a diminished oxygen saturation was present in both arterial and venous blood. The arterial (anoxic) anoxemia may be accounted for by the edema and passive congestion at the bases of the lungs, the venous (stagnant) anoxemia by the insufficient circulation. Oxygen inhalation raised the saturation of the arterial and venous blood to the normal level. The elevation of the arterial oxygen content naturally causes a corresponding elevation of the venous content, the respiratory exchange taking place at a higher level. In addition to this relative increase of venous oxygen, there was an additional increase that seems best explainable on the basis of an improved blood flow. The relative permanency of the elevated venous saturation tested at frequent intervals over a period of several days is further evidence that the circulation was improved by the increased supply of oxygen. The objective changes were in a measure confirmatory. The cyanosis disappeared for several days at a time. The pulse when regular was slowed. When the heart was under the influence of digitalis or of the phases of periodic respiration, the changes were more complicated. The periodic respiration was temporarily changed to regular respiration by the inhalation of oxygen. However, in two out of three trials, the mere application of the mask connected with room air was sufficient to cause regular respiration. No significant change in blood pressure, vital capacity, urinary secretion, or carbon dioxide content of arterial and venous blood resulted from oxygen inhalation in the amount given. The electrocardiographic changes indicate a lesser degree of block during during and following the administration of oxygen. Subjectively, he usually said that his breathing was better or that he felt more comfortable, but he was never enthusiastic. It seemed that the mask contributed somewhat to lessening his sense of relief, as it was often hot and wet with perspiration at the end of the administration.

Case 4 (Table 2).—G. W., colored, male, fireman; age, 57 years.

Diagnosis.—Cardiac insufficiency, syphilitic aortitis, aortic regurgitation, right hydrothorax.

History.—Rheumatism at 7, chancre at 23. In good health up to four years ago, when dyspnea, palpitation of heart and cough first occurred. During the months before admission he suffered from increasing dyspnea and orthopnea, massive edema of extremities and progressive distention of abdomen.

Physical Examination.—Oct. 4, 1920. Periodic respiration alternated with frank dyspnea. No cyanosis of mucous membranes. Heart much enlarged, downward and to the left. Blowing diastolic murmur over aortic area, and systolic murmur at apex; rate, 88. Corrigan and capillary pulse. Blood pressure, 190/60. Dulness and moist râles at bases of lungs, with diminution of breath sounds on right. Massive edema of extremities. Abdomen distended, no free fluid. Liver not felt. Urine showed a trace of albumin, specific gravity from 1.019 to 1.030. Phenolsulphonephthalein excretion 45 per cent. in two hours. Nonprotein nitrogen, 30 mg. per 100 c.c. Blood Wassermann strongly positive.

Course and Treatment.—Confined to bed; restricted fluids; digipuratum from October 6 to 8, in all 8 grains; evening sedative of morphin or veronal.

October 7: Patient in hospital three days with no change in physical signs, or any improvement in comfort. Oxygen was given through a mask attached to rebreathing apparatus for one-half hour. Oxygen saturation of arterial blood before administration, 87.6 per cent.; after, 99 per cent. Venous saturation before, 71 per cent.; after, 78.5 per cent. Pulse 84 before, 82 after. Respiration 34 before, 40 after. Objectively there were no other changes. Immediately after administration, he said he felt about the same. In the evening he felt distinctly better and thought the oxygen had helped him. Sleep was better that night than previously.

October 8: Decided diuresis occurred. Urinary output increased from 360 to 960 c.c., with an intake less than usual, 480 c.c., instead of the average daily intake of 800 c.c. Digipuratum had been given on three previous days, 8 grains in all.

October 10: Patient slightly irrational. Marked bradycardia and vomiting resulted from digitalis. Pulse, though regular, had been brought from 88 to 48. He was very uncomfortable. Oxygen was given through mask for one-half hour. Venous saturation before, 57.3 per cent.; at the end of fifteen minutes, 86 per cent.; at the end of thirty minutes, 91.4 per cent. Periodic respiration was replaced after one minute's oxygen by regular rapid respiration, rate 40 per minute. Pulse remained low, between 45 and 50. Subjective response was that he felt a little sleepy at the end of the administration. No diuresis followed.

October 22: His course has been apparently stationary. He showed at this time most of the evidences of cardiac insufficiency that he did on admission, including persistence of lung signs. The oxygen saturation of the arterial blood was 89.9 per cent., the venous saturation 69.4 per cent. He was removed to his home on the following day. He died there one month later.

In this case of decompensated syphilitic heart disease, the arterial (anoxic) anoxemia was fully corrected by the inhalation of oxygen. The venous saturation, within normal limits after three days' rest in bed, was increased by oxygen inhalation. The marked slowing of the heart due to digitalis was attended with a fall in venous saturation, apparently to the degree of a stagnant anoxemia, and suggests that the use of digitalis in regular hearts to the point of marked slowing causes a diminution in circulatory efficiency.

Case 5 (Table 2).—M. T., white, male, tailor; age, 68 years.

Diagnosis.—Cardiac insufficiency; chronic myocarditis; auricular fibrillation; auriculoventricular block; right bundle branch block; emphysema; chronic bronchitis; polyserositis.

History.—No rheumatic or venereal history. For many years previous to 1911, he took two glasses of brandy daily. During the past thirteen years he

has suffered from cough and dyspnea, which have gradually but progressively become worse, until now he is practically bedridden. Cyanosis has been evident for five years. His abdomen has been tapped repeatedly for four years, at first every three months, now every three weeks. He lives at home, coming to the hospital only for paracentesis.

Physical Examination.—Eight years ago he had an enlarged, regular heart without evidence of valvular disease, enlarged liver and spleen, emphysema and chronic bronchitis. His heart is now of huge size, extending into the mid-axilla. Electrocardiographic tracings have shown progressive changes, first a lengthening of the P-R interval, then right bundle branch block (slight alteration in the arteriogram, and finally auricular fibrilation. The other conditions also advanced, but to a less degree. The cyanosis was the most striking feature of the case, and he was called "the blue man."

Nov. 9, 1920: At rest on a couch, he was moderately dyspneic. Ears, cheeks and nose were a reddish blue, lips a dark, deep blue, hands a bluish bronze color. The tips and borders of his tongue were purple. He was able to lie flat for two and one-half minutes, after which he became very uncomfortable. Lying flat was attended with an even greater degree of cyanosis. Oxygen was given through a mask for two five-minute periods, but he complained that it suffocated him. The rubber mouthpiece was then tried (for the first time) and he breathed through it readily. This was given for twenty minutes, the nostrils held occluded most of the time. The ears and nail-beds of the fingers pinkened slightly. The cheeks and hands were still markedly cyanotic, though less so than previously. The lips were still darkly cyanotic. The venous oxygen saturation before the administration was 29.6 per cent., twenty minutes after it was 82.4 per cent. Venous carbon dioxid content was 58.4 volume per cent. before, 47.4 volume per cent. twenty minutes after. Pulse (no deficit) from 50 to 64 before; from 54 to 66 after. Respiration, from 24 to 26 before, 28 after. Blood pressure, 115/55 before; 112/56, after. Vital capacity of the lungs 1,026 c.c. and 1,222 c.c. before; 1,110 c.c. after. Urine acid before, alkaline one-half hour later. Electrocardiogram showed auricular fibrillation and right bundle branch block. After oxygen, the notching of the R wave was less marked, and the height of the R wave was lowered. After the inhalation the patient (without any questioning) expressed decided increase in his general comfort and in his breathing.

November 18: Patient was seen in his home. He had an acute exacerbation of his chronic bronchitis. Respiration was accompanied by much wheezing. Sibilant and sonorous râles heard throughout both chests. Cyanosis very marked. Abdomen was more distended with fluid. Oxygen was given through the mouthpiece. A Douglas bag had been previously filled with a 60 per cent. oxygen mixture, and left at the bedside in place of an oxygen tank. A two-way valve was inserted in the circuit, and patient gave oxygen to himself, twice a day for forty-five minutes at a time. This was repeated on the following day.

November 20: Cyanosis noticeably diminished by oxygen of two previous days. Dyspnea was still present, and abdomen was accumulating more fluid. Oxygen was again given as before, except that a 75 per cent. oxygen mixture was supplied. Breathing was again described by the patient as "easier" after oxygen. Cyanosis was strikingly diminished in hands and ears, and finger nails were slightly pink. Lips were still blue, though less so than previously. Arterial oxygen saturation before today's inhalation was 86.3 per cent.; one hour after, 95.6 per cent. Venous saturation, 46.4 per cent. before; two days later, 57.8 per cent. The arterial carbon dioxid content was 47.7 volume per cent. before, 49.9 volume per cent. one hour later. The venous carbon dioxid content was 53.2 volume per cent. before, and 53 volume per cent. two days later. Pulse 60 before treatment, 48 one hour later; respiration 22 before, 23 one hour later.

November 22: No oxygen given for two days. Acute bronchitis largely dissipated. Color like that one hour after oxygen two days ago. Abdomen distended with fluid and respiration was difficult. Arterial saturation 97.8 per cent., venous saturation 57.8 per cent. Arterial carbon dioxid content 52.6 volume per cent.; venous carbon dioxid content, 53 volume per cent. Pulse 50, respiration 24.

November 24: Patient seen after paracentesis. Felt much relieved. Breathing better after removal of fluid. Fingers and hands showed only slight cyanosis. He said his hands had not been so free from cyanosis for years and reiterated that the oxygen treatment at his home made him much more comfortable and improved his breathing.

Patient was not treated further with oxygen. He continues to come to outpatient clinic for paracentesis.

This case is an example of chronic arterial (anoxic) and venous (stagnant) anoxemia, the former element being due to emphysema, chronic bronchitis, and passive congestion at the bases of the lungs, and the latter to a slowed, insufficient blood flow. It is a striking illustration of the fact that a severe lack of oxygen, even of anoxic type, may last for years without disastrous effects, if it supervenes very gradually. The saturation of the arterial and venous blood was raised to the normal by the administration of oxygen. The venous saturation in auricular fibrillation changes from minute to minute depending on the output from the heart, but the change in these experiments was too great to be accounted for in this way. The difference in color of the blood before and after oxygen, from an almost black to a bright red, was more striking in this case than in any of the others studied. A certain amount of permanency in the raised oxygen content of the blood and in the clinical improvement occurred. The electrocardiographic changes again involving intraventricular block may, perhaps, indicate a lesser degree of block during oxygen administration. It is interesting that the cyanosis was only little altered after the first single administration of oxygen, but became definitely relieved after continued administration, although in each case the blood values showed great improvement.

Case 6 (Table 2).—L. J., white, male, cabinet maker; age, 62 years.

Diagnosis.—Myocardial insufficiency; auricular fibrillation; cardiac hypertrophy.

History.—No rheumatic, tonsillar, or venereal history. Ten years ago, first suffered from dyspnea on exertion, palpitation and precordial pain. Never had edema of extremities. Three subsequent attacks occurred. Present break in compensation is similar to previous ones.

Physical Examination.—March 21, 1921. Face deeply flushed. Lips red, with cyanotic overcast. Finger nails, cheeks and ears slightly cyanotic. No dyspnea at rest. Heart markedly enlarged, completely irregular, without murmurs. Blood pressure, 170/100. Moist râles at both bases; diminished breath sounds at right base, and bronchovesicular breathing at left back below angle of scapula. Liver edge palpable 5 cm. below costal margin. Urine: specific gravity, from 1.014 to 1.020; very slight trace of albumin. Blood

Wassermann negative. Nonprotein nitrogen, 41.4 mg. per 100 c.c. Phenolsulphonephthalein excretion, 35 per cent. in two hours. Red blood cell count, 6,100,900. Hemoglobin, 154 per cent. (oxygen capacity). Vital capacity, 1,754 c.c.

Course and Treatment.—Confined to bed, salt-free low protein diet; convallaria, 5 c.c., three times a day, March 25 and 26 (used in a separate investigation).

March 25, 1921: Condition unchanged. Vital capacity 1,866 c.c. Oxygen given through mouthpiece for one-half hour. Oxygen saturation of the arterial blood before the inhalation, 86 per cent.; after, 98.1 per cent.; venous saturation before, 53.4 per cent.; after, 47.8 per cent. Arterial carbon dioxid content before, 40.3 volume per cent.; after, 41.3 volume per cent.; venous carbon dioxid content before, 48.2 volume per cent.; after 49.9 volume per cent. The cyanosis gradually cleared, leaving the lips deep red, and giving an increased pinkness to rest of face. No change of a consistent nature occurred in cardiac, pulse, or respiratory rate. Electrocardiographic tracings showed auricular fibrillation unchanged, before and after. The patient said he felt better after the inhalation. He breathed about 80 per cent. oxygen. The cyanosis began to return directly after the administration, and in half an hour was again marked, not seemingly to the degree before oxygen. On the following day, no effect of the oxygen inhalation could be seen clinically. Vital capacity, 1,474 c.c.

March 29: Condition unchanged. No dyspnea at rest. Cyanosis was not definitely altered. Arterial oxygen saturation 88.3 per cent.; venous saturation, 58 per cent. Arterial carbon dioxid content, 42.7 volume per cent. Oxygen was given through a mouthpiece for one hour, patient breathing about 50 per cent. oxygen. Clinical effects were similar to previous administration. Blood not tested. Vital capacity before oxygen, 1,726 c.c.; day after oxygen, 1,838 c.c.

Patient left the hospital two weeks later. Seemed to have less dyspnea on exertion. Cyanosis was still present, a little less marked. Signs in lungs largely persisted.

The exact diagnosis of this patient remained in doubt. The signs in the lungs were those of passive congestion, and apparent compression of the left lower lobe from the large heart. The anoxemia was both arterial (anoxic) and venous (stagnant), and of marked degree in proportion to the other symptoms. The chronic nature of the diminished oxygen content of the blood was manifested by the polycythemia. Inhalation of oxygen completely relieved the arterial anoxemia, though only temporarily. The lowered venous content of oxygen can be explained by the varying output from the heart occurring in auricular fibrillation. Lundsgaard [5] showed that the venous oxygen content in auricular fibrillation may be normal in the stage of decompensation, and also that it might be abnormally lowered in full compensation. It is obvious that the venous saturation cannot be used as a criterion of oxygen therapy when the auricles are fibrillating.

CASE 7 (Table 2).—S. M., white, housewife; age, 68 years.

Diagnosis (necropsy).—Cardiac insufficiency; cardiac hypertrophy and dilatation; pulmonary edema; pulmonary thrombus.

History.—Shortness of breath and fatigue for two years. Two months before entry, patient began to suffer from a sense of suffocation, and pronounced dyspnea and orthopnea. Swelling of legs and ankles, continued nausea, and general weakness caused her to enter the hospital.

Physical Examination.—Oct. 25, 1920: Dyspneic and orthopneic. Slight cyanosis of mucous membranes. Lungs, anteriorly and posteriorly, filled with fine and medium moist râles. Heart much enlarged, downward and to left. Sounds muffled, regular, without murmurs. Blood pressure, 190/110. Pulse full and bounding; rate 78; no thickening of radial artery. Veins of neck extremely distended. Fluid wave and shifting dulness in abdomen. Massive leg edema. Phenolsulphonephthalein excretion 30 per cent. in two hours. Non-protein nitrogen 40 mg. per 100 c.c. of blood. Urine, specific gravity, from 1.020 to 1.022; trace of albumin; occasional cast. White blood cells, 17,000; polymorphonuclears, 90 per cent. Blood Wassermann, negative.

Course and Treatment.—Confined to bed; fluids restricted to 800 c.c.; digipuratum, October 25 to 28, in all 20 grains.

Oct. 27, 1920: Condition unchanged. Patient was very restless and anxious. Arterial saturation, 90.7 per cent.; venous saturation, 69 per cent. Arterial carbon dioxid content, 39 volume per cent.; venous carbon dioxid content, 45.2 volume per cent.

October 28: Dyspnea continued. Face was of a grayish dusky color, with moderate cyanosis of the lips. Râles in lungs were of coarse moist variety. Arterial saturation, 88 per cent.; venous saturation, 74.5 per cent. Arterial carbon dioxid content, 43.5 volume per cent.; venous carbon dioxid content, 46.5 volume per cent. Oxygen was given through a mask connected with a Douglas bag containing a 60 per cent. oxygen mixture. Three fifteen-minute periods were given, separated by five-minute intervals. Patient took the mask poorly, and it was stopped because of the discomfort it gave her. One-half hour later, the arterial saturation was 90.9 per cent.; the arterial carbon dioxid content, 43 volume per cent. No improvement in color, respiration, pulse or distention of neck veins was observed. On questioning, she said she breathed easier after the oxygen. She was then given pure oxygen for three five-minute periods, after which the administration was finally stopped because of patient's discomfort in breathing through a mask. Pulse 90 before oxygen, 104 after. Respiration 27 before, 36 after. Vital capacity, 672 c.c., before; 450 c.c. after. Blood pressure, 205/118 before; 210/120 after. There seemed to be the very slightest alleviation of the cyanosis of the lips as a result of the oxygen. No further administration was attempted. She became increasingly cyanotic, and died at five the next morning.

At necropsy a large hypertrophied and dilated heart was found, without evidence of valvular disease. There was sclerosis of the aorta, pulmonary and renal arteries. In branches of the right pulmonary artery leading to the inferior lobe of the right lung, grayish-red thrombus masses were seen, with corresponding areas of lung infarction. The lung tissue of both lungs was moist, leathery, and of a salmon pink color. The trachea and bronchi were bathed in muco-pus.

The anoxemia in this case was of the anoxic type, arising obviously from the congestion and edema of the lungs. This was not successfully overcome by oxygen in the period given, although it was partially relieved. The mask was so disturbing to the patient as to render its use impossible, and accounts for the elevation in pulse and respiration. (The mouthpiece had not been thought of at the time this patient was studied.)

Case 8 (Table 2).—J. V., white, housewife; age, 50 years.

Diagnosis.—Cardiac insufficiency, rheumatic mitral valvular disease; chronic myocarditis; auricular fibrillation; pulmonary edema. (At necropsy, deformity of the mitral, tricuspid and aortic valves, elevated fibrous plaque at beginning of right coronary artery were found.)

History.—Tonsillitis, followed by rheumatism, when 23 years old. For past sixteen years patient has had dyspnea on exertion. Nine days ago, was abruptly seized with palpitation of heart and dyspnea, followed the day after by substernal pain, vomiting, sleeplessness and weakness.

Physical Examination.—Oct. 19, 1920: Marked dyspnea and orthopnea. No cyanosis. Heart greatly enlarged, completely irregular, with systolic and diastolic murmurs at apex and at aortic area. Apex rate, 140; pulse rate, 128. Blood pressure, 120/85. Lungs clear. Liver not palpable. Slight edema over tibia. Urine: specific gravity, from 1.026 to 1.028; slight trace of albumin. Blood Wassermann, negative. Phenolsulphonephthalein excretion, 20 per cent. in two hours. Nonprotein nitrogen 60 mg. per 100 c.c. Electrocardiogram showed auricular fibrillation, left ventricular preponderance.

Course and Treatment.—Confined to bed; soft solids; digifolin 4 c.c., and digipuratum 9 grains, from Oct. 19 to 26, 1920; evening, sedatives of morphin.

Oct. 26, 1921: Course in hospital showed no improvement. On the previous night, restlessness and insomnia being unrelieved, hyoscin hydrobromid, 0.01 grain, was given. In the morning she was in coma, and outspoken edema of the lungs was present. Frothy mucus filled the mouth and throat. Face was a dusky gray; lips, hands and finger nails were deeply cyanotic. Respiration was moderately deep, rate 37. Pulse was scarcely palpable, completely irregular, and very rapid. Veins were collapsed. Oxygen saturation of the arterial blood was 76.1 per cent. Arterial carbon dioxid, 39.2 volume per cent. Because of agonal condition of patient, oxygen administration was not delayed to get venous saturation. Pure oxygen was given through a mask for two hours and twenty minutes. At the end of forty minutes the venous saturation was 43.8 per cent., taken while she was breathing oxygen. The venous carbon dioxid content was 52.2 volume per cent. No change clinically could be observed. At the end of one hour, the pulse became temporarily palpable, but quickly tapered off into a thready run which could not be counted. At the end of two hours, it became palpable for several minutes. At this time the lips showed a distinct diminution of cyanosis, and there was less cyanosis in the fingers and hands. No change in breathing was observed, and frothy mucus continued to collect in the back of the throat. Arterial oxygen saturation was 97.7 per cent.; the arterial carbon dioxid content, 45.7 volume percent. At the end of two hours and twenty minutes the venous saturation was 59 per cent., the venous carbon dioxid content 55.2 volume per cent. The administration was then stopped. Face, lips, hands, finger nails, and upper portion of chest speedily became a deep blue, and she died twenty minutes later.

In this case, a severe arterial (anoxic) anoxemia was caused by widespread edema of the lungs; the venous (stagnant) anoxemia was caused by acute heart failure. Cyanosis showed no distinct relief until oxygen had been given for two hours. Arterial saturation at that time showed that the oxygen content of the arterial blood had been raised to the normal. The long time that was required to alleviate the cyanosis was a surprising feature. The abundance of foam and mucus in the bronchial tree and the existence of a venous anoxemia are probably accountable for this, since the former delayed the passage of the oxygen and the latter masked the improvement. The elevation of the venous saturation is probably largely explained by the raising of the arterial saturation. The carbon dioxid content of arterial and venous

blood steadily rose, indicating that the edema fluid hindered the respiratory exchange in the lungs. An acidosis was probably present, due to carbon dioxid accumulation.

Case 9 (Table 2).—H. R., colored, male, janitor; age, 45.

Diagnosis.—Cardiac insufficiency; chronic myocarditis; asthma; chronic bronchitis; pulmonary edema.

History.—No rheumatic or syphilitic history. One pint of whisky daily for many years. Shortness of breath and cough began three years ago. During the past six weeks cough, dyspnea and discomfort have been extreme, and extremities became swollen.

Physical Examination.—Feb. 3, 1921: Marked dyspnea, respirations rapid and shallow; rate 45; moderate cyanosis of mucous membranes. Lungs full of sibilant, sonorous and medium-sized moist râles, more in front than back. Heart much enlarged. Sounds regular, rapid, poor quality. No murmurs. Blood pressure, 145/105. Vessel wall palpable. Liver dulness extends to umbilicus in right midclavicular line. Moderate leg edema. Urine: specific gravity, from 1.012 to 1.020; albumin, slight trace. Phenolsulphonephthalein excretion, 50 per cent. in two hours. Nonprotein nitrogen, 74.1 mg. per 100 c.c. Blood Wassermann, negative.

Course and Treatment.—Confined to bed; fluids restricted to 1,500 c.c.; digitalis leaves, 2 grains, three times a day; evening sedatives. Patient's course was stationary for seven days, and then took a sudden change for the worse.

Feb. 10, 1921: He was found comatose in the early morning. Respirations rapid and shallow, rate 45. Lips and mucous membranes quite cyanotic. Pupils pin-point, and react very slightly to light. Pulse 128, small, easily compressible. Heart sounds not heard because of gurgling noises during respiration. Lower half of anterior chest is filled with medium and coarse moist râles, posteriorly moist râles are scattered throughout.

Oxygen was administered through the Haldane mask, at the rate of four liters per minute for fifteen minutes. No change in condition was observed, and rebreathing apparatus was substituted, with valve attachment to the mask affording about 80 per cent. oxygen. One-half hour later patient was bled 500 c.c. Oxygen was kept up for three hours. Pulse had gradually fallen to 100; respirations varied between 36 and 44; cyanosis had disappeared. Patient at times moved about in bed, opened his eyes, and showed signs of returning consciousness. After oxygen had been administered for forty-five minutes the arterial blood showed a saturation of 100 per cent.; the venous saturation was 53.6 per cent. Arterial carbon dioxid content was 75.0 volume per cent.; venous carbon dioxid content, 82.4 volume per cent. The pulse rate remained down the rest of the day, and there was no cyanosis.

February 11: Patient looked much better in the morning. He was still dyspneic, but cyanosis was absent. He seemed rational and answered questions. Moisture in lungs continued. In the afternoon he swiftly became very cyanotic, dyspneic, and finally comatose. The oxygen saturation of his venous blood was 0.3 per cent.; the carbon dioxid content, 63.4 volume per cent. Oxygen was administered as on the previous day. Cyanosis was much diminished, though still present. Pulse slowed from 112 to 100. Oxygen was stopped after two hours, and patient died one hour later.

Asthma, bronchitis, and edema of the bases of the lungs were responsible for the arterial (anoxic) anoxemia. The development of general pulmonary edema introduced a very grave state of oxygen want. The inhalation of oxygen plus venesection tided him over for one day. On the following day, a sudden recurrence of anoxemia,

largely due to cardiac failure and shown strikingly in the venous saturation, was only partially relieved by oxygen. Death occurred one hour after oxygen was stopped, due apparently to cardiac failure.

DISCUSSION

It is interesting to note that all of the patients had an arterial (anoxic) anoxemia, which we must attribute to the associated pulmonary conditions. Most of them had a stagnant type of anoxemia, which can be attributed directly to the insufficient output from the heart. The cases, it may be observed, were selected usually because of the presence of cyanosis and do not represent all varieties of cardiac insufficiency, since in some cyanosis is entirely absent.

These cases showed uniformly an increase in the oxygen saturation of the arterial blood following short periods of oxygen inhalation. When passive congestion and edema were localized at the bases, or in the presence of acute bronchitis or chronic bronchitis and emphysema, the relief of arterial (anoxic) anoxemia was comparatively prompt. When widespread edema of the lungs was present, more prolonged administration of oxygen was required to elevate the arterial saturation.

The mechanism of elevation of the arterial saturation seems to depend on the increased diffusion pressure of oxygen available in oxygen-rich mixtures. In the cases in which passive congestion and edema are confined to the bases, the arterial anoxemia arises presumably because the swelling and edema in the alveolar wall act as a hindrance to the normal diffusion of oxygen.

In widespread edema of the lungs, the fluid in the alveoli and bronchial tree inhibits the free passage of air. In acute bronchitis, excess moisture in the bronchi and bronchioles acts in a similar way. These hindrances to the normal exchange of oxygen are apparently overcome by an increased diffusion pressure of oxygen. A second factor to be considered in the elevation of the arterial saturation is the shallow character of the pulmonary ventilation and the related diminution of the vital capacity of the lungs that occurs in cardiac insufficiency. Shallow breathing, although brought about by anoxemia, is itself a cause of anoxemia.[34] That this plays any great rôle in the production of the anoxemia of heart disease or in its alleviation is at present in doubt. In this series, no significant changes in rate of respiration occurred, except in the change from periodic to regular breathing. Beddard and Pembrey[35] found a decrease in pulmonary ventilation

34. Haldane, J. S.; Meakins, J. C., and Priestley, J. G.: The Effects of Shallow Breathing, J. Physiol. **52**:449, 1919.

35. Beddard, G. P., and Pembrey, M. S.: Observations on Pulmonary Ventilation in Disease, Brit. M. J. **2**:580, 1908.

during oxygen inhalation in four cases of cardiac failure, without change in rate. If this is a constant occurrence, oxygen inhalation does nothing in the way of removing shallow breathing, but merely increases its effectiveness. According to Haldane, Meakins and Priestley,[34] however, shallow breathing may arise in heart disease with impaired circulation as a direct result of the anoxemia. In their experiments on normal individuals it was found that shallow breathing caused uneven ventilation of the lungs, which in turn caused anoxemia, periodic respiration and other symptoms. These effects were made worse when the subject assumed the recumbent position, and this was made the basis of the explanation of orthopnea in cardiac insufficiency. They state that "since the orthopnea is due to shallow breathing caused by and intensifying anoxemia, it is clear that the condition can be treated by adding oxygen to the air inspired." In the cases of our series, it frequently seemed that the breathing was deeper during oxygen inhalation, but since no exact measurements were made no conclusions can be drawn, and it remains for further investigation to determine the precise rôle of shallow breathing in heart disease. It is our impression that it may augment a previously existing arterial anoxemia, but that it is not ordinarily of the extent to be the primary cause.

Periodic respiration has been considered a manifestation of slight degrees of oxygen want. In these cases, it was constantly changed to regular breathing by oxygen administration. However, immediately after the mask was removed, with the blood still normally saturated with oxygen, the periodic respiration usually recurred. Further, it was sometimes changed to regular respiration by the application of the mask connected with the room air. Although oxygen deficiency is probably its essential cause, there are other factors such as the patient's attention and habit, which operate in its continuance.

Cardiac dyspnea in the cases studied seemed to have little relation to the degree of anoxemia, either anoxic or stagnant. Further, the inhalation of oxygen, although it completely relieved the anoxemia, produced only slight or moderate relief of the dyspnea. In accordance with these facts, we hold the belief, expressed by previous investigators, that lack of oxygen is not the important cause of cardiac dyspnea, even in the presence of marked cyanosis. It seems rather to be regarded as an important and dangerous byproduct. The carbon dioxid contents of the arterial and venous blood in three cases showed a decrease in alkali reserve, and in two cases an apparent increase. As a result of oxygen therapy, there was frequently a slight increase in carbon dioxid content. In a recent study of the carbon dioxid dissocia-

tion curve in cardiac decompensation, Peters [36] expresses the belief that the cause of the dyspnea is the fact that a greater ventilation is necessary to effect the normal carbon dioxid elemination, with the additional factors in some cases of a carbon dioxid acidosis (with actual lowering of the p_H), and in others a reduction of the available alkali of the blood. In four tested cases, an increase in the normal difference between the arterial and alveolar carbon dioxid tension was found. That an inefficient pulmonary mechanism for the exchange of the blood carbon dioxid is at the basis of cardiac dyspnea is indeed strongly suggested by Peters' work. That a mechanical factor, the diminution of the vital capacity emphasized by Peabody,[37] is the important cause of the inefficient pulmonary ventilation involves, it seems to us, a necessary addition to the theory of cardiac dyspnea.

The venous saturation was regularly increased by oxygen inhalation except in one case of auricular fibrillation. In this condition, the varying output from the heart results in a variable venous saturation, which, therefore, becomes an unreliable criterion for oxygen therapy, just as it is of circulation efficiency. The elevation of the venous saturation in the main represented and was due to the elevation in arterial saturation, the respiratory exchange taking place on a higher level. In addition to this relative increase of venous oxygen, there was in three cases a further increase that seems best explained on the basis of an improved blood flow. In two cases tested at frequent intervals, the elevated venous saturation had a certain degree of permanency, which again suggested that the circulation was bettered by the increased supply of oxygen. The relief of the cyanosis and the slowing of the pulse were in a measure confirmatory.

It must be recognized that a venous saturation below 65 per cent. does not indicate that the circulation is impaired, unless the arterial saturation is normal. In order to determine whether there is circulatory defect, the difference between the arterial and venous saturation must be obtained and compared with the normal difference. If it is increased, an inefficient circulation is indicated. This difference has been emphasized by Means and Newburgh [4] as the significant determination in the estimation of blood flow from oxygen values, and was first discussed by Krogh and Lindhard [38] and termed by them the coefficient of utilization of the oxygen carrying power. The normal

36. Peters, J. P., and Barr, D. P.: The Carbon Dioxid Dissociation Curve and the Carbon Dioxid Tension of the Blood in Cardiac Dyspnea, J. Biol. Chem. **45**:559, 1921.

37. Peabody, F. W., and Wentworth, J. A.: The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443, 1917.

38. Krogh, A., and Lindhard, J.: Measurements of the Blood Flow Through the Lungs of Man, Skand. Arch. f. Physiol. **27**:100, 1912.

range is between 20 and 30 per cent., since the normal arterial saturation is about 95 per cent. and the venous saturation between 65 and 75 per cent. The determination of cardiac insufficiency on the basis of the oxygen unsaturation in volume per cent. or the oxygen consumption in volume per cent., introduces a factor which has little relation to blood flow, namely, hemoglobin. The upper limit of normal for these values has been placed by Lundsgaard [5] and Harrop [8] at 8 volume per cent. Now, if a patient's hemoglobin registers 43 per cent. according to the Haldane scale, his oxygen capacity is only 8 volume per cent. In order for him to show any cardiac insufficiency on this standard the oxygen unsaturation would have to be over 8 volume per cent., which is manifestly impossible as he does not possess

TABLE 1.—Effect of Oxygen on the Blood Gases in Two Normal Individuals *

Case No.	Diagnosis	Date, 1920	Oxygen Inhalation	Oxygen Content		Oxygen Saturation		Oxygen Capacity Vol. %	Hemoglobin Calculated from Oxygen Capacity	Carbon Dioxid Content	
				Arterial Vol. %	Venous Vol. %	Arterial %	Venous %			Arterial Vol. %	Venous Vol. %
1	Normal	11/18	Before oxygen	.....	11.52	....	67.7	17.03	92.1	....	51.3
			Oxygen for 30 min.	.....	11.78	....	69.1	(17.03)	(92.1)	....	53.0
2	Normal	10/ 6	Before oxygen	16.79	12.38	96.6	71.3	17.38	94.0		
			Oxygen for 30 min.	17.30	12.64	99.6	72.8†	(17.38)	94.0		
	Normal	12/15	Before oxygen	.....	14.63	....	73.5	19.92	107.9	....	52.4
			Oxygen for 30 min.	.....	16.51	....	83.0	(19.92)	(107.9)	....	50.2

* Subject in recumbent position.
† At end of oxygen administration wrist was tightly bandaged at site of artery puncture, and hence venous blood in this instance was under stasis when drawn.

the available hemoglobin. For an estimation of blood flow, then, the venous unsaturation in volume per cent. would be accurate only to individuals with a normal hemoglobin, whereas the venous saturation in per cent. and the coefficient of utilization would hold good for all patients since it gives the relative usage of the hemoglobin.

The slowing of the pulse that occurred in the normal individuals occurred to a greater extent in the presence of anoxemia. Slowing of the heart in normal men was first observed by Smith [39] and recently carefully confirmed by Benedict and Higgins.[29] The blood pressure and vital capacity showed no immediate relation to oxygen deficiency or its correction. The electrocardiogram in the normal and in a case of uncomplicated auricular fibrillation showed no alteration. In two

39. Smith, H. A.: The Effect of Oxygen Inhalation on the Pulse, Med. Rec. **1**:481, 1871.

TABLE 2.—Effect of Oxygen Inhalation on the Blood Gases in Seven Cases of Cardiac Insufficiency

Case No.	Diagnosis	Date	Oxygen Inhalation*	Oxygen Content		Oxygen Saturation		Oxygen Capacity Vol. %	Hemoglobin Calculated from Oxygen Capacity	Carbon Dioxid Content		Remarks
				Arterial Vol. %	Venous Vol. %	Arterial %	Venous %			Arterial Vol. %	Venous Vol. %	
3	Cardiac insufficiency; chronic myocarditis; partial heart block; right bundle branch block	10/16/20	4 hrs. before oxygen...	16.52	10.05	87.5	53.2	18.90	102.1	....	....	Periodic respiration
			Before oxygen.....	.....	8.16	....	41.6	19.62	106.1			
			Oxygen for 30 min.	19.51	13.41	99.5	68.4	(19.62)	(106.1)	....	....	Regular respiration
			15 min. after oxygen...	.....	13.21	....	67.4	(19.62)	(106.1)			
		10/20/20	Before oxygen.....	18.29	11.73	83.5	53.7	21.88	118.2	....	....	Periodic respiration
			Oxygen for 15 min.	.....	15.60	....	71.6	(21.88)	(118.2)	....	....	Regular respiration
			Oxygen for 30 min.	.....	15.81	....	72.4	(21.88)	(118.2)	....	....	Regular respiration
			1½ hrs. after oxygen....	19.68	15.81	89.9	72.4	(21.88)	(118.2)	....	....	Periodic respiration
		10/21/20	24 hrs. after oxygen....	.....	15.91	....	78.1	20.40	110.1	....	61.4	Periodic respiration
		10/23/20	.....	.....	12.55	....	66.1	19.00	102.8	....	....	Periodic respiration
		10/25/20	Before oxygen.....	18.27	14.62	96.6	77.4	18.90	102.1	56.2	61.0	Periodic respiration
			40 min. after oxygen...	17.94	.....	97.7	....	18.39	99.4	59.2	....	Periodic respiration
		11/ 1/20	No oxygen — apnea	15.44	.....	85.2	....	18.12	98.0	56.7	....	Acute bronchitis developed
			dyspnea.....	15.78	.....	87.0	....	.....	.....	59.3	....	Cyanosis +++
			No oxygen.....	.....	9.73	....	53.6	(18.12)	(98.0)	....	65.1	
		11/ 3/20	Before oxygen—apnea	15.76	.....	78.3	....	20.17	108.9	61.4	....	Cyanosis +++
			dyspnea.....	17.14	.....	85.2	....	(20.17)	(108.9)	62.0		
			Oxygen for 30 min.	.....	19.03	....	94.5	(20.17)	(108.9)	....	61.0	Cyanosis 0
4	Cardiac insufficiency; syphilitic aortitis; aortic regurgitation; right hydrothorax	10/ 7/20	Before oxygen.....	15.70	12.72	87.6	71.0	17.90	97.1	....	....	After 3 days in bed
			Oxygen for 30 min.	17.71	14.04	99.0	78.5	(17.90)	(97.1)			
		10/10/20	Before oxygen.....	.....	11.62	....	57.3	20.31	109.8	....	....	Excess of digitalis
			Oxygen for 15 min.	.....	17.45	....	86.0	(20.31)	(109.8)			
			Oxygen for 30 min.	.....	18.53	....	91.4	(20.31)	(109.8)			
		10/22/20	No oxygen.....	14.16	10.91	89.9	69.4	15.77	85.2			
5	Cardiac insufficiency; chronic myocarditis; auricular fibrillation; auriculoventricular block; right bundle branch block; emphysema; chronic bronchitis	11/ 9/20	Before oxygen.....	.....	6.32	....	29.6	21.32	115.1	....	58.4	
			20 min. after oxygen...	.....	17.58	....	82.4	(21.32)	(115.1)	....	47.4	Oxygen for one-half hour
		11/20/20	Before oxygen.....	18.24	9.83	86.3	46.4	21.18	114.2	47.7	53.2	Oxygen given on 2 previous days
			1 hr. after oxygen.....	18.64	.....	95.6	....	19.50	105.2	49.9		
		11/22/20	48 hrs. after oxygen....	18.64	10.90	97.8	57.8	18.80	102.0	52.6	53.0	
6	Myocardia insufficiency auricular fibrillation	3/25/21	Before oxygen.....	24.56	15.23	86.0	53.4	28.54	154.3	40.3	48.2	
			5 min. after oxygen....	27.99	13.60	98.1	47.8	(28.54)	(154.3)	41.3	49.9	Oxygen for one-half hour
		3/29/21	No oxygen.....	23.34	15.33	88.3	58.0	26.45	143.0	42.7	63.8	Patient bled 300 c.c. day previous
7	Cardiac insufficiency; pulmonary edema; pulmonary thrombus	10/27/20	No oxygen.....	19.14	14.53	90.7	69.0	21.10	114.0	39.0	45.2	
		10/28/20	Before oxygen.....	19.14	16.20	88.0	74.5	21.79	117.6	43.5	46.5	
			Oxygen for 45 min.	19.79	.....	90.9	....	(21.79)	(117.6)	43.0		
8	Cardiac insufficiency; rheumatic mitral valvular disease; chronic myocarditis; pulmonary edema	10/26/20	Before oxygen.....	16.38	.....	76.1	....	21.5?	116.1	39.2	....	Cyanosis ++++
			Oxygen for 40 min.	.....	9.43	....	43.8	(21.50)	(116.1)	....	52.2	Cyanosis ++++
			Oxygen for 2 hrs.	20.14	.....	97.7	....	20.60	111.2	45.7	....	Cyanosis ++
			Oxygen of 2 hrs. 20 min.	.....	12.14	....	59.0	(20.60)	(111.2)	....	55.2	Cyanosis +
9	Cardiac insufficiency; chronic myocarditis; asthma; chronic bronchitis; pulmonary edema	2/10/21	Oxygen for 45 min.	19.14	10.01	100.00	53.6	18.70	101.0	75.0	82.4	Cyanosis relieved by oxygen
		2/11/21	Before oxygen.....	.....	0.06	....	0.3	19.88	107.2	....	63.4	Cardiac failure

The term "before oxygen" refers only to the day of the blood determination. It indicates that the blood for analysis was drawn before any oxygen therapy of the day, and that oxygen was subsequently given on the same day. "Oxygen for — min." indicates that the blood was taken immediately or a short time after oxygen therapy. All other terms as well, such as "no oxygen," refer solely to the day of the determination. For the precise relation of oxygen inhalation to the blood determination, as well as for the complete duration of the therapy, the text must be consulted. The parenthesis ( ) about the figure for the oxygen capacity indicates that the determination preceding was used.

† There was apparently an excess of oxygen in physical solution, 0.44 vol. %.

cases of right bundle branch block, one with and one without auricular fibrillation, a decreased notching and a diminished height of the R wave was present during the inhalation of oxygen.

The question of the effect of oxygen on renal function is being additionally investigated. No definite action on the quantity of urine eliminated was discerned in the short periods in which oxygen was given.

SUMMARY

1. In a normal man, the inhalation of oxygen for one-half hour caused an increase in the oxygen saturation of the arterial and venous blood. In a second normal individual, the inhalation of oxygen for the same period caused a very slight rise in the venous saturation, the arterial saturation not being tested. The pulse was slowed in both cases. No significant changes occurred in the blood pressure, vital capacity, electrocardiogram, venous carbon dioxid content, or rate of respiration.

2. In seven cases of cardiac insufficiency, an anoxic (arterial) anoxemia was present in all, a stagnant (venous) anoxemia in all except one.

3. Oxygen inhalation regularly increased the arterial saturation. Where the anoxic anoxemia seemed due to passive congestion and edema at the bases of the lungs, the arterial saturation was raised to the normal by inhalation of oxygen for one-half hour. In the cases complicated by widespread pulmonary edema, relief of arterial anoxemia was accomplished in from forty-five minutes to two hours.

4. Oxygen inhalation increased the venous saturation in all except one case of auricular fibrillation. The elevation of the venous saturation was largely due to the raising of the arterial saturation. In a few cases, there was an additional and somewhat permanent increase in the venous saturation that seems best explained on the basis of an improved blood flow resulting from the increased supply of oxygen.

5. The arterial anoxemia of acute and chronic bronchitis, and emphysema, occurring in cardiac insufficiency, was fully relieved by oxygen inhalation. The venous saturation was correspondingly elevated.

6. The relief of the cyanosis and the slowing of the pulse were the outstanding objective changes. The blood pressure, vital capacity, arterial and venous carbon dioxid content, urinary excretion, and rate of respiration showed no definite changes from short periods of oxygen inhalation. The electrocardiogram showed consistent changes in two cases of right bundle branch block, no change in one uncomplicated

case of auricular fibrillation. Subjectively, the patients usually said they felt more comfortable or that their breathing was better, but they were rarely enthusiastic.

We wish to express our thanks to Dr. James H. Means for his invaluable aid during the work reported in this and the following two papers, and for his kind assistance in the preparation of the manuscript. We are greatly indebted to Dr. Donald D. Van Slyke and Dr. William C. Stadie who showed us the combined method of gas analysis before it was published, and to Dr. Paul D. White for his aid in obtaining and analyzing the electrocardiograms.

STUDIES IN OXYGEN THERAPY

II. IN PNEUMONIA AND ITS COMPLICATIONS *

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In the previous paper, a report was made of the effect of oxygen on two normal individuals and seven cases of cardiac insufficiency. This paper represents a continuance of the studies in oxygen therapy in ten cases of lobar pneumonia and two cases of bronchopneumonia. The theoretical indications for giving oxygen, the methods employed, and the recent pertinent literature have been outlined in the beginning of the first paper. The plan of investigation has been maintained, namely, the correlation of the clinical condition of the patient with the oxygen saturation of the arterial and venous blood before and after treatment.

REPORT OF CASES

The individual cases follow:

CASE 10[1] (Table 3).—M. W., white, male, driver, 36 years.

Diagnosis.—Lobar pneumonia; chronic pulmonary tuberculosis; edema of the lungs.

History.—Mother and sister died of tuberculosis. Patient has suffered from a chronic productive cough for five years. Three days before entry, tiredness, headache, and sharp pain in left chest began. Two days later, cough increased in intensity, sputum resembled prune juice, and weakness became marked.

Physical Examination.—Jan. 29, 1921 (fourth day of disease): Temperature, 103.0 F.; pulse, 138; respiration, 32. Very poor nutrition. Moderate dyspnea. Marked cyanosis of nail beds. Consonating râles over entire left chest. Dulness and diminished breath sounds at left base. Dulness and bronchovesicular breathing below right clavicle. Heart not enlarged. Sounds regular, rapid, good quality, without murmurs. Artery wall palpable. Blood pressure, 115/80. Urine, negative. Blood Wassermann, negative. White blood cells, 37,400; polymorphonuclears, 90 per cent. Blood cultures (two), sterile. Sputum, pneumococcus subtype II. Sputum for tubercle bacilli positive.

Course and Treatment.—Routine pneumonia treatment (force fluids; soft solids; evening sedatives, usually morphin). Digitalis leaves, 1 grain, three times a day from Feb. 1 to 15, 1921.

Jan. 31, 1921 (sixth day of disease): Temperature, 102.3 F.; pulse, 130; respiration, 30. Dyspnea and cyanosis as on admission. Patient mentally alert

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* From the Medical Service of the Massachusetts General Hospital.

* This paper is No 16 of a series of studies of the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

The expense of this work was in part defrayed by a grant from the Proctor Fund of Harvard University for the study of Chronic Diseases.

1. The cases in the three papers are numbered serially.

and rational. Arterial oxygen saturation, 77.2 per cent., venous saturation, 50.2 per cent. Arterial carbon dioxid content, 49.5 volume per cent.; venous carbon dioxid content, 53.1 volume per cent. Carbon dioxid dissociation curve showed a slight acidosis.[2]

February 1 (seventh day of disease): Temperature, 101.0 F.; pulse, from 116 to 120; respiration, 32. Patient appeared distinctly worse. Increased dyspnea and cyanosis. Oxygen was given for one-half hour through the mouthpiece. He breathed about half through his mouth and half through his nose, thus utilizing about a 60 per cent. oxygen mixture. The cyanosis distinctly lessened, though it did not wholly disappear. The pulse slowed to 108, returning five minutes after administration to its previous rate of from 116 to 120. The respiratory rate also slowed, oscillating between 22 and 26, and remaining at 24 for one-half hour after oxygen. The cyanosis largely returned five minutes after oxygen, and seemed completely returned at the end of ten minutes. Two hours later, the arterial oxygen saturation was 75.9 per cent.; the venous saturation, 60.1 per cent.; arterial carbon dioxid content, 62.8 volume per cent.; venous carbon dioxid content, 67.0 volume per cent.

February 2 (eighth day of disease): Temperature, 102.5 F.; pulse, 150; respiration, 44. Patient seemed in agonal state. He lay propped up in bed, head thrown back, eyes closed, and in stupor. There was a coarse gurgle in his throat during respiration. Lips were cyanotic, nail beds were dark deep blue, and backs of hands had a dusky leaden color. Breathing was [illegible] from 40 to 45 per minute, regular. Lungs showed outspoken general edema. Besides the coarse bubbling sounds, there were many fine and medium moist râle throughout both chests. Pulse small and thready, rate varying between 140 and 160. Oxygen was given through the mouthpiece, patient breathing about 50 per cent. oxygen. In fifteen minutes, the lip cyanosis had largely disappeared, and the blue color in the nail beds had changed to a light heliotrope shade. For one hour and twenty minutes, there was no discernible improvement in pulse or respiration. After an hour and thirty-five minutes, the oxygen was stopped for twelve minutes and blood was taken for analysis. During this period the cyanosis in the nail beds recurred to the extent before oxygen, although no cyanosis appeared in the lips. The arterial saturation was 62.3 per cent.; the venous saturation, 53.5 per cent. Arterial carbon dioxid content was 60.4 volume per cent. The carbon dioxid dissociation curve showed a marked uncompensated carbon dioxid acidosis. (The arterial saturation was not determined immediately before oxygen.). Oxygen was then continued almost uninterruptedly to make a total duration of two hours and twenty minutes. The pulse began to slow after one hour and twenty minutes, and at the end of the administration was 120, of good volume and tension. Respiration slowed to 34, seemed deeper, and accompanied by much less dyspnea. (See Table 1 for effect on pulse and respiration.) The cyanosis was markedly lessened though not completely absent in the nail beds. During the administration the patient became wakeful and cognizant of his surroundings, and at the end was mentally alert, said he felt good, and was eager for more oxygen. Throughout the day, oxygen was given for about twenty to thirty minutes every hour. The cyanosis decreased during the administrations, and recurred after them. The pulse and respiration showed no further slowing. The coarse gurgle in his throat disappeared, though moist râles were still present everywhere in his lungs. That night he was given 15 gm. sodium bicarbonate. Oxygen was continued through the night, thirty to forty minutes every two hours.

February 3 (ninth day of disease): Temperature, 102.4 F.; pulse, 124; respiration, 38. Patient continued to manifest improvement. Dyspnea and cyanosis distinctly less. Cyanosis was now of a light heliotrope shade without

2. The work on the carbon dioxid dissociation curve in pneumonia will be reported elsewhere by A. L. Barach, W. N. Woodwell and J. H. Means.

oxygen, almost clearing with oxygen. Pulse was of good quality. Oxygen was given fifteen minutes every hour during the day and every two hours at night. Arterial saturation after one of these periods was 82.2 per cent.; venous saturation, 78.4 per cent. Arterial carbon dioxid content was 66.7 volume per cent., venous carbon dioxid content, 70 volume per cent. Carbon dioxid dissociation curve was on a higher level than on previous day, and showed no acidosis.

February 4-8: Temperature gradually fell to 99.0 F.; pulse and respiration fell more slowly to 110 and 30, respectively. Lungs became resonant throughout, with fewer râles. Cyanosis became less marked, but persisted in absence of oxygen. Oxygen was given less often, from twenty minutes every one or two hours to twenty minutes every two or three hours. The cyanosis almost cleared during oxygen, but always reappeared afterward; at times the pulse slowed during oxygen and at times no effect was evident. Slowing was more apt to occur when the patient had not had oxygen for a considerable time previous. February 8, oxygen was given for fifteen minutes by the Haldane apparatus, in which oxygen was supplied through a mask at the rate of four liters per minute, and for a similar period by the mouthpiece rebreathing apparatus, in which about 50 per cent. oxygen was breathed by the patient. With the Haldane apparatus

TABLE 1.—Effect of Oxygen in Lobar Pneumonia with Pulmonary Edema in Case 10

	Pulse	Respiration	Cyanosis
Before oxygen	140-160	40-45	++++
Oxygen for 5 minutes	140	40	++++
Oxygen for 10 minutes	145	40	++++
Oxygen for 15 minutes	145	40	+++
Oxygen for 25 minutes	100	45	+++
Oxygen for 35 minutes	Indeterminate	45	+++
Oxygen for 45 minutes	144	40	++
Oxygen for 55 minutes	140	38	++
Oxygen for 1 hour	142	..	++
Oxygen for 1 hour 20 minutes	128	30	++
Oxygen for 1 hour 30 minutes	126	40	++
Oxygen for 1 hour 40 minutes	130	38	+++
Oxygen for 2 hours	122	36	++
Oxygen for 2 hours 10 minutes	126	38	++
Oxygen for 2 hours 20 minutes	120	34	++

Cyanosis began to diminish after fifteen minutes' oxygen inhalation, pulse and respiration after one hour and twenty minutes. Patient breathed about 50 per cent. oxygen through the mouthpiece. Arterial saturation, 62.4 per cent.; venous saturation, 53.5 per cent.; arterial carbon dioxid content, 60.4 volume per cent. (Blood tested one hour and forty-seven minutes after oxygen was begun, the previous twelve minutes having been without oxygen.)

no effect on the pulse rate was produced. With the mouthpiece rebreathing method, the pulse slowed from 108 to 111 before to 102 after (Table 4). The cyanosis likewise diminished sooner and to a greater extent when the patient was breathing 50 per cent. oxygen. The rebreathing bag was kept full by two liters of oxygen per minute so that less oxygen was actually used in this method though offered to the patient in greater concentration. (The Haldane gauge was connected with the rebreathing apparatus for this measurement.)

February 8-15: Patient's temperature again rose and oscillated between 100 and 101 F.; pulse, from 100 to 110; respiration, from 27 to 35. Numerous tubercle bacilli were found in the sputum. It was evident that residual process (râles in right chest) was active tuberculosis. A very faint cyanosis persisted in nails. February 14 oxygen was given and electrocardiograms were taken before, during and after oxygen. No change in pulse or electrocardiographic tracings occurred. He proved to be a morphin habitué, and when morphin was finally withheld he left the hospital. He became progressively weaker and more emaciated, and died at home Feb. 27, 1921.

This patient seemed to have a lobar (pneumococcus) pneumonia in the presence of active pulmonary tuberculosis. He recovered from the pneumonia, but eventually succumbed to the tuberculosis. On admission, he had an arterial (anoxic) anoxemia. The lowered venous saturation did not represent a stagnant circulation, since the relation between arterial and venous oxygen content was normal. (A lowered arterial saturation of necessity reduces the venous saturation, the respiratory exchange taking place at a lower level.) The administration of oxygen by partially relieving the arterial anoxemia brought the venous saturation within normal limits. When edema of the lungs developed, the pulse became extremely rapid and feeble. At that time a true venous (stagnant) anoxemia was undoubtedly present, along with the arterial

TABLE 2.—EFFECT OF OXYGEN AS GIVEN BY HALDANE APPARATUS AND AS GIVEN BY MOUTHPIECE REBREATHING METHOD IN CASE 10

	Pulse	Respiration	Cyanosis
Haldane Apparatus: 4 liters oxygen per min.			
Before oxygen	108-111	28-32	+++
Oxygen for 1 minute	108	28	+++
Oxygen for 2 minutes	108	30	+++
Oxygen for 3 minutes	111	30	++
Oxygen for 4 minutes	108	30	++
Oxygen for 5 minutes	108	30	++
Oxygen for 8 minutes	108	30	++
Oxygen for 10 minutes	108	32	+
Oxygen for 13 minutes	108	30	+
Oxygen for 15 minutes	108	30	+
15 minutes without oxygen	108	27-33	+++
Rebreathing Apparatus: 50% oxygen			
Oxygen for 1 minute	111	33	+++
Oxygen for 2 minutes	108	33	++
Oxygen for 3 minutes	105	33	++
Oxygen for 4 minutes	108	33	+
Oxygen for 5 minutes	105	36	+
Oxygen for 8 minutes	102	36	+
Oxygen for 10 minutes	105	33	+
Oxygen for 13 minutes	102	33	+
Oxygen for 15 minutes	102	30	+
10 minutes without oxygen	102-105	33-36	++
15 minutes without oxygen	108	33	+++

With the patient breathing for fifteen minutes through the Haldane apparatus, in which 4 liters of oxygen per minute were added to the inspired air, no effect was produced in the pulse rate. During a period of the same length, with patient breathing about 50 per cent. oxygen through the mouthpiece, the pulse distinctly slowed. The cyanosis also decreased more quickly with the mouthpiece method.

anoxemia. Because of what seemed an agonal condition of the patient, oxygen therapy was begun immediately, and no blood was withdrawn for analysis until the pulse had definitely improved. The venous saturation was then almost normal, although an arterial anoxemia still existed. On the following day, the arterial saturation showed a marked increase, though it did not reach normal limits. The effect of a single administration of oxygen accomplished little in this case; the effect of long continued and frequently repeated inhalations of oxygen brought the patient from an obviously moribund condition to one of relative safety, and produced striking improvement in pulse, breathing, color, comfort, and mental condition of the patient, and, apparently, an actual improvement in pulmonary edema.

The fact that the pulse did not slow after oxygen administration for fifteen minutes with the Haldane apparatus and definitely slowed when given with the rebreathing method for the same period is attributable to the higher percentage of oxygen breathed in the latter method. Benedict and Higgins[3] found no material change in the pulse rate of normal men when the oxygen inhaled was raised to 40 per cent. A slight, though noticeable, slowing in the pulse occurred when 60 per cent. oxygen was breathed, and a very positive slowing when 90 per cent. oxygen was administered.

Case 11 (Table 3).—A. M., white female, clerk; age 29 years.

Diagnosis.—Lobar pneumonia.

History.—Two days before entry, headache, pains in back and legs, nausea and vomiting began. The same day, patient had a shaking chill, followed by cough, reddish-brown sputum, and pain in right chest.

Physical Examination.—Nov. 22, 1920 (third day of disease): Temperature, 104.0 F.; pulse, 112; respiration, 40. Moderately prostrated and dyspnéic. No cyanosis evident. At right posterior chest, below spine of scapula, dulness, bronchial breathing and voice, and crepitant râles were present. Slight dulness at left base. Heart not enlarged, soft systolic murmur at apex. Blood pressure, 120/65. Sputum inoculation, pneumococcus type II. Blood culture gave a pneumococcus in one flask; second flask, sterile. White blood cells, 19,200; polymorphonuclears, 71 per cent. Blood Wassermann, negative. Urine, sp. gr. from 1.010 to 1.030; slight trace of albumin; no casts.

Course and Treatment.—Routine pneumonia treatment. Nov. 24, 1920 (fifth day of illness): Signs on admission unchanged. Patient was moderately prostrated, rational and quiet. Oxygen saturation of arterial blood, 98.8 per cent.; venous saturation, 66.0 per cent.; arterial carbon dioxid content, 53 5 volume per cent, venous carbon dioxid content, 56.3 volume per cent. Carbon dioxid dissociation curve was within normal limits. Oxygen was given for thirty minutes through the mouthpiece. Nose was occluded most of the time by keeping fingers loosely over nostrils. During the administration, she lay quietly and comfortably, eyes closed most of the period. Face definitely pinkened at the end of the inhalation, without discernible change in hands or nail beds. Directly after, she said she could breathe better and that the pain in the chest was a little better. One hour later she told the nurse she felt wonderfully better and asked when the oxygen was to be given again. The venous saturation five minutes after oxygen was 74.6 per cent.; the venous carbon dioxid content, 57 volume per cent. The pulse was 100 before and 100 after oxygen.

November 25 (sixth day of illness): Temperature, 103 F.; pulse, 120; respiration, 40. Patient more prostrated than yesterday. Right side of face flushed, remainder colorless. The nails were slightly cyanotic. Respirations were rapid, shallow, with loud grunting expiration. She was quiet and rational, but complained of weakness, and a new sharp pain in the left chest. Lungs showed an extension of bronchial breathing to left posterior chest. Arterial saturation 90.8 per cent.; arterial carbon dioxid content, 52.9 volume per cent. Oxygen was given through the mouthpiece, connected with a Douglas bag containing seven liters of an 80 per cent. oxygen mixture. After twenty minutes, patient said she felt tired and administration was stopped. (Nose was held occluded during the inhalation). Face showed increased pinkness; lips had better color, and it was doubtful whether the nails had any cyanosis.

3. Benedict, F. G., and Higgins, H. L.: Effects on Men at Rest of Breathing Oxygen-Rich Gas Mixtures, Am. J. Physiol. **28**:1, 1916.

Breathing seemed easier, with less grunting, during and after oxygen. Rate before oxygen, 44; after, 42. Pulse before, from 125 to 130; after, 120. Two hours later she said she felt better and stronger after the inhalation. Oxygen was again given in the evening for twenty-five minutes, this time without holding the nose and connected with tank. She breathed about 80 per cent. oxygen. Pulse before oxygen, 128, after oxygen, 120. Five minutes later 124, two hours later, 120, five hours later, 120. Respirations 38 before, 34 after; five minutes later from 36 to 38; two hours later, 32; five hours later (asleep) 30.

November 26 (seventh day of illness): Temperature, 102 F.; pulse, 110; respiration, 30. Patient felt better and looked better. Moderately dyspneic, but without expiratory grunt. No discernible cyanosis. Arterial oxygen saturation, 99.7 per cent., arterial carbon dioxid content, 61 volume per cent. Frank signs of consolidation persist over both lower lobes. Oxygen was given through mask for twenty minutes. The soda-lime can was kept in ice water, so that the rebreathing air was cooled. Pulse before oxygen 100, after oxygen 100, one-half hour later 100. Respiration 34 before, after 28, one-half hour later 32. Patient noticed no striking change but thought she could breathe better after the inhalation.

No further oxygen was given. Temperature persisted high, between 101 and 102 F. for nine more days, reaching normal on the 16th day of illness. She left the hospital three weeks later, lungs clear. Patient spoke repeatedly of the relief oxygen afforded her.

On the fifth day of illness, patient had no anoxemia. The administration of oxygen produced distinct subjective improvement but no change in pulse or respiratory rate. The venous oxygen saturation was raised. On the sixth day an extension of the pneumonic process occurred to the left lung, and an arterial anoxemia was present. Oxygen was given twice that day. Pulse was distinctly slowed after each administration, respiratory rate after the second. Subjective relief was again experienced and the following morning no anoxemia was present. Oxygen was again given but without effect on pulse and with slight slowing of respiration. In this case the slowing of the pulse occurred when the patient was anoxemic and not when the blood was normally saturated.

Case 12 (Table 3).—D. H., white, male, chauffeur; age 21 years.

Diagnosis.—Lobar pneumonia. Pulmonary edema.

History.—For six days patient had a slight cold with cough. On the sixth day he was awakened from sleep by a severe pain in right side, felt chilly, began to cough frequently and raised rusty sputum. Entered the hospital the same day.

Physical Examination.—Feb. 24, 1921 (first day of disease): Temperature, 103.4 F.; pulse, 128; respiration, 48. Moderate dyspnea. Very slight cyanosis of nail beds. Lungs showed dulness and a friction rub at right base. Heart without enlargement, murmurs, or irregularity. Pulse full and bounding. Urine negative. Blood culture sterile. Sputum inoculation showed pneumococcus type I. White blood cells 22,000; polymorphonuclears, 88 per cent.

Course and Treatment.—Routine pneumonia treatment. Serum therapy. On the third day of illness, 100 c.c. of pneumococcus I serum was given; on the fourth day, 100 c.c. of serum was given in the morning and 100 c.c. in the evening. No improvement resulted in the prostration of the patient, the temperature, pulse, or respiration, and on the morning of the fifth day he was strikingly worse.

February 28 (fifth day of disease): Temperature, 103.5 F.; pulse, from 140 to 150; respiration, from 35 to 40. Marked prostration and dyspnea. Patient stuporous. Finger-nails deeply cyanotic, lips and ears a bluish-red color. Signs of consolidation had extended to left lower lobe, and many coarse moist râles were present throughout both lungs. White blood cells had dropped to 11,000. Oxygen saturation of the venous blood was 63.5 per cent.; venous carbon dioxid content, 51.7 volume per cent. Arterial blood was not tested, but the deep cyanosis was of necessity due to a marked lowering of the arterial saturation, since no venous anoxemia was present. Oxygen administration was attempted with the Haldane apparatus, but the patient struggled against the mask, and it had to be given up. The mouthpiece was substituted, and he breathed through it in comfort, using about 40 per cent. oxygen. His condition steadily improved. At the end of two hours continuous inhalation his color, pulse, breathing, and mental reaction showed decided betterment. Pulse rate before oxygen, from 136 to 140; after two hours, from 124 to 128. Respiration, 30 before, 28 after. Cyanosis became markedly diminished, although it did not wholly disappear. Oxygen was given for six more times during the day and evening, each time for about half an hour. The pulse during oxygen was usually 128; in the periods between oxygen, 132. The cyanosis reappeared during the intervals between oxygen, though not to the extent present in the morning, becoming diminished correspondingly during the inhalation. Serum was given that afternoon, at midnight, and the next morning, 100 c.c. each time.

March 1 (sixth day of disease): Temperature, from 102.5 to 100.2 F.; pulse, from 128 to 100; respiration, 30. Patient manifested continued improvement. Prostration, dyspnea and cyanosis were much lessened. Oxygen had been given eight times through the night up to twelve o'clock noon, in periods varying from twenty minutes to one hour. Blood analysis then showed an arterial saturation of 88.9 per cent. and a venous saturation of 64.5 per cent.; arterial carbon dioxid content, 53 volume per cent.; venous carbon dioxid content, 55.5 volume per cent. Oxygen was given four times more during the day and evening. The temperature began to fall at midnight of the fifth day, and gradually fell during the sixth day, reaching 100.5 F. at midnight, apparently a slow crisis.

March 2-3 (seventh and eighth days of disease): Temperature, 100.0 to 101.0 F.; pulse, 110 to 100; respiration, 28 to 24. Although the crisis was over, patient appeared dull and weak and felt tired. Slight but definite cyanosis persisted in the finger-nails. Oxygen was given four times March 2 and once March 3, each time for about one-half hour. March 3, the arterial saturation after oxygen was 93 per cent. The coarse moist râles disappeared anteriorly but were still numerous at both bases posteriorly. The cyanosis disappeared completely three days later, the temperature became flat on the following day, and the patient left the hospital ten days later feeling well and with lungs clear.

In this patient, the development of pulmonary edema on the fifth day of the disease seemed to indicate a fatal outcome. The continued inhalation of oxygen produced a striking improvement in the clinical picture and greatly relieved the arterial anoxemia. Slight lowering of the arterial saturation persisted after oxygen administration and for five days after the crisis. Oxygen inhalation in this case relieved a condition of acute oxygen want which might otherwise have proved disastrous.

CASE 13 (Table 3).—A. A., white, male, carpenter; 26 years.

Diagnosis.—Lobar pneumonia.

History.—Five days before admission, patient had a chill, and since then has felt hot, feverish and weak. The next day he developed cough and blood tinged sputum. For past three days he has had a sharp pain in right chest, worse on inspiration.

Physical Examination.—Jan. 5, 1921 (fifth day of disease): Temperature, 104 F.; pulse, 100; respiration, 36. Moderate dyspnea. Slight cyanosis of finger-nails. Dulness, bronchial breathing, and crepitant râles over right posterior chest below angle of scapula. Dulness and coarse moist râles at left base. Heart sounds faintly heard, no murmurs. Pulse full and not rapid. Premature ventricular contraction occurred once in every six or ten beats (electrocardiogram). Moderate jaundice of sclera and skin. Urine, sp. gr., from 1.018 to 1.034; occasional slight trace of albumin and occasional cast; bile for five days. White blood cells, 15,000; polymorphonuclears, 83 per cent. Blood culture sterile. Blood Wassermann negative. Sputum inoculation gave a pneumococcus type I. Arterial oxygen saturation, 92.4 per cent.; arterial carbon dioxid content, 42 volume per cent. Carbon dioxid dissociation curve showed an uncompensated carbon dioxid acidosis.

Course and Treatment.—Routine pneumonia treatment. No serum therapy. Digitalis leaves, 1½ grains, twice a day, January 5-7, 1921.

January 6 (sixth day of disease): Temperature, from 104 to 105 F., pulse, from 100 to 130; respiration, from 30 to 45. Patient little changed. Oxygen was commenced with the mouthpiece, but patient inhaled mostly through his nose and blew out through the tube. He did not understand English, and procedure could not be explained to him. The mask was then adjusted connected to the rebreathing bag, and this he took fairly well; duration of administration, twenty minutes. Arterial saturation before oxygen 94.3 per cent.; four minutes after, 98 per cent.; venous saturation before, 79.5 per cent.; arterial carbon dioxid content before, 44.3 volume per cent.; after, 44.8 volume per cent. Carbon dioxid dissociation curve gave evidence of a carbon dioxid acidosis. Immediately after oxygen was begun, a striking slowing of the pulse occurred, from 116 to 92. When oxygen was temporarily stopped, it rapidly mounted to its former rate. This process could be duplicated at will, and it was found that the following occurrence was fairly constant: After ten seconds oxygen, the pulse rate was 108; after twenty-five seconds, 92 or 88; after oxygen was withdrawn for fifteen seconds, the pulse had risen to 108, after thirty seconds, to 116. As long as the inhalation was continued the pulse was from 88 to 92. In addition, the premature contractions which occurred every six to eight beats previously were absent during oxygen inhalation. The respirations remained 44 throughout. The finger-nails showed no certain change in color. Subjectively, the patient noticed no change.

January 7 (seventh day of disease): Temperature, from 104.2 to 105.4 F.; pulse, from 110 to 128; respiration, from 35 to 44. Condition unchanged. It was attempted to give oxygen and follow cardiac changes with the electrocardiograph. Patient, however, struggled against the mask. Oxygen given for fifteen minutes showed no change in pulse rate, electrocardiographic tracings, or in respiratory rate. The oxygen saturation of the arterial blood before the inhalation was 96.5 per cent.; arterial carbon dioxid content, 45.3 volume per cent.

Two days later crisis occurred and patient speedily recovered.

January 18: Patient well. Arterial saturation 96.5 per cent.; arterial carbon dioxid content, 50.6 volume per cent. Carbon dioxid dissociation curve showed no acidosis.

In this case a very slight arterial anoxemia was fully corrected by the inhalation of oxygen. During the first administration, a remarkable slowing of the pulse occurred, lasting only as long as oxygen was given. It is possible that this was not a direct oxygen effect but of vagal origin due to the increased depth of breathing. The arterial blood was normally saturated on the day following the inhalation. No subjective improvement occurred.

Case 14 (Table 3).—L. M., white, male, salesman; age 42 years.

Diagnosis.—Lobar pneumonia; empyema; pyopneumothorax; chronic alcoholism (necropsy).

History.—Whiskey for years. One pint daily in past year. Four days ago following exposure to wet he had a shaking chill. On the next day he had generalized pains, cough, and sputum. Two days ago he began to have pain in left side and marked dyspnea.

Physical Examination.—Nov. 27, 1920 (fourth day of disease): Temperature, 105 F.; pulse, 140; respiration, 45. Marked dyspnea with grunting expiration, extreme restlessness and pleuritic pain. Face and neck deeply flushed. Cheeks had a bluish tinge. Lips and finger-nails deeply cyanotic. Dulness, bronchial breathing and many medium moist râles over left lower lobe. Crepitant râles at right base. Heart sounds rapid, without murmurs. Pulse of poor quality, rate 140. Slight distention of abdomen. Urine, sp. gr., from 1.028 to 1.038; slight trace of albumin; frequent granular casts. Blood Wassermann, strongly positive. White blood cells 20,800; polymorphonuclears, 90 per cent. Blood culture, sterile.

Course and Treatment.—Routine pneumonia treatment. Chest swathe worn throughout illness.

November 29, 1920 (sixth day of disease): Temperature, 103 F.; pulse, 138; respiration, 44. Condition essentially the same as on admission. Oxygen was given for twenty minutes through a loosely fitting mask. Patient was uncomfortable, and inhalation had to be frequently interrupted. Respiration became deeper and slower during administration, rate 36 before, from 30 to 32 during, 36 after. Pulse, from 140 to 144 before and during administration. Lips seemed to have a trifle better color after oxygen but no change was observed in the cyanosis of the nails. Oxygen saturation of the venous blood before the inhalation 52.6 per cent.; after, 56 per cent. After oxygen breathing seemed to have less of the grunting character. Patient thought he could breathe easier after the oxygen but was not enthusiastic. In the evening oxygen was given through the mouthpiece for twenty-five minutes. He breathed easily and comfortably, using about 60 per cent. oxygen. Respiration became deeper and slower; rate before, 44; during, from 26 to 34; five minutes after, 44. Pulse before, 155; during, 144; five minutes after, 150. It was not possible to decide about any change in color.

November 30 (seventh day of disease): Temperature, 102 F.; pulse, 135; respiration, 40. Patient in great distress because of pleuritic pain and dyspnea. Lips were very blue. Finger-nails, backs of hands, and ears were slightly cyanotic. Arterial oxygen saturation, 74.4 per cent.; venous saturation, 54.8 per cent.; arterial carbon dioxid content, 47 volume per cent. Carbon dioxid dissociation curve showed an uncompensated carbon dioxid acidosis. Oxygen was given through the mouthpiece for twenty minutes. Lips seemed a trifle less cyanotic, nail-bed cyanosis unchanged. Pulse before, from 152 to 155; during, 148; after, from 150 to 155. Respiration, from 48 to 50 before, from 36 to 48 during, from 44 to 48 after. Breathing seemed less arduous after oxygen, and patient said he felt more comfortable. Oxygen was given three times more that day, in fifteen minute periods. He complained of feeling tired after the last inhalation.

December 1 (eighth day of disease): Temperature, from 101 to 103 F.; pulse, 150; respiration, 40. Dyspnea and pleuritic pain continued unabated. Cyanosis of nails seemed less marked, lips still deeply cyanosed. Venous saturation 32.2 per cent. Oxygen was given for fifteen minutes through the mouthpiece eight times during the day. The pulse slowed slightly each time, returning to previous rate when the inhalation was stopped. The respiratory rate remained unaffected, but the breathing seemed deeper. Color and comfort little changed.

December 2 (ninth day of disease): Temperature, 101 F.; pulse, 140; respiration, 36. Dyspnea and cyanosis less marked. Pulse still rapid, compressible, poor quality. Oxygen was given as on previous day for three times in the morning and three times in the afternoon, and blood tested at 1:30 p. m. Arterial saturation, 91.6 per cent.; venous saturation, 36 per cent.; arterial carbon dioxid content, 47.2 volume per cent.; venous carbon dioxid content, 53.7 volume per cent. Carbon dioxid dissociation curve showed no acidosis.

December 3 (tenth day of disease): Temperature, from 102 to 104 F.; pulse, 148; respiration, 35. Cyanosis diminished in lips and nail beds. General condition about the same. Oxygen given for fifteen minutes twice in the morning and twice in the afternoon and blood tested at noon. Venous saturation, 46.1 per cent.

December 4-5 (eleventh and twelfth days of disease): Temperature, from 99.5 to 104 F.; pulse, 140; respiration, from 30 to 40. Condition was little changed. No oxygen was given. Cyanosis did not increase.

December 6 (thirteenth day of disease): Temperature 105 F.; pulse, 140; respiration, 40. There was slight cyanosis of the lips and barely perceptible cyanosis of nail beds. Arterial saturation, 92.7 per cent.; venous saturation, 57.8 per cent.; arterial carbon dioxid content, 40.6 volume per cent.; venous carbon dioxid content, 49.2 volume per cent. Oxygen was given through a mask with valve attachment for twenty minutes. The venous saturation immediately after was 58 per cent., the venous carbon dioxid content, 50 volume per cent. The respiration before the administration was 40 per minute, during the administration from 32 to 36, and five minutes after, 40. The pulse varied between 140 and 144, and was unchanged by the treatment. There seemed to be a very slight diminution of the lip cyanosis, but no other change in color. The patient said he felt no relief during the inhalation, but directly afterward felt fine. One-half hour later chest puncture revealed purulent fluid, the culture of which subsequently showed staphylococcus, streptococcus, and gram negative bacilli. That night the patient died.

In the beginning, the patient had a severe arterial (anoxic) anoxemia, with only a relative lowering of the venous saturation. In the middle of his course, a true venous (stagnant) anoxemia developed and became the dominant feature of his illness. This paralleled a pulse of a persistently poor quality and rapid rate. Toward the end, the arterial anoxemia became markedly diminished, and later the venous anoxemia was much reduced. The patient was obstreperous during his entire illness. He resisted taking the mask, but took the mouthpiece for short periods very well, complaining, however, of long periods. Inhalation of oxygen, in this case, caused no immediate increase in oxygen saturation of the venous blood. The arterial saturation increased under oxygen administration, but it is possible that much of this improvement was due to changes in the lungs. No arterial determinations were done immediately before and after an inhalation.

After oxygen had been given at repeated intervals for two days, an increase from 74.4 to 91.6 per cent. occurred. The cyanosis showed only a very slight to a doubtful clearing during the administration, though in the above two days it gradually diminished. It is possible that the venous anoxemia present at this time was responsible for the persistence of the cyanosis during the administration, and that the continued oxygen inhalations did have an influence in the raising of the arterial saturation. However, this case was exceptional in the fact that oxygen inhalation (even 80 per cent. oxygen) had so little effect on the cyanosis. To some extent this can be ascribed to the fact that there was a marked venous anoxemia due to the insufficient circulation and in part to an arterial anoxemia due to a blood flow through an area of consolidation. The pulse was usually temporarily slowed. The respiration likewise, was as a rule, slowed. The patient said that he felt better after the treatments, but that it did not last. His final fatal outcome was attended with only a slight anoxemia, both arterial and venous, and was due to empyema sepsis. The carbon dioxid dissociation curve showed an acidosis which disappeared with the diminution in arterial anoxemia.

Case 15 (Table 3).—T. B., white, male, longshoreman; age 47 years.

Diagnosis.—Lobar pneumonia; empyema.

History.—Four days before admission he had a sudden chill followed by inspiratory pain in left chest, feverishness and weakness. Two days later he began to cough, spit up blood tinged sputum and became for a time delirious.

Physical Examination.—Nov. 28, 1920 (fourth day of disease): Temperature, 104 F.; pulse, 100; respiration, 40. Dyspnea without cyanosis. Over lower half of left chest anteriorly and posteriorly there were dulness, bronchial voice and breath sounds with few crepitant râles. At right base posteriorly, dulness, diminished breathing and crepitant râles present. Heart sounds regular, good quality, no murmurs. Pulse full and not rapid. Sputum inoculation, pneumococcus I; blood culture, pneumococcus I. White blood cells 16,400; polymorphonuclears, 68 per cent. Urine, sp. gr., from 1.008 to 1.025; trace of albumin. Blood Wassermann negative.

Course and Treatment.—Routine pneumonia treatment. No serum therapy.

December 3, 1920, (ninth day of disease): Elevated temperature, pulse and respiration, and moderate prostration continued. Thoracentesis of left chest revealed 42 c.c. cloudy yellow fluid, from which pneumococcus I in pure culture was recovered. Aspiration of left chest done daily thereafter and small amounts of opaque yellow fluid removed.

December 7 (thirteenth day of disease): Temperature had fallen to 100.5 F. Patient appeared and felt weak. Cheeks were deeply sunken. Face had a slight reddish flush, without actual cyanosis. Fingers were pale. Lung signs same as on admission, except for egophony at left base. Pulse, 100; respiration, 25. Oxygen saturation of arterial blood 88.9; arterial carbon dioxid content, 49 volume per cent.

December 8 (fourteenth day of disease): Temperature, 99 F. Appearance same as yesterday. Said he felt dazed. Oxygen was given through mouthpiece for twenty minutes, patient using about an 80 per cent. oxygen mixture. Felt perfectly comfortable, but noticed no change in his condition. No cyanosis was evident previous to administration and no increased pinkness occurred after it.

Respiratory rate 24 before and after, but increased depth seemed to be present. Pulse 96 before, 92 after, 92 one-half hour later. Arterial saturation immediately before 85.5 per cent.; immediately after, 100 per cent.; arterial carbon dioxid content 47 volume per cent.

December 9 (fifteenth day of disease): Temperature 99 F. Appearance unchanged. Felt "pretty good, but weak." Arterial saturation, 96.6 per cent.; venous saturation, 88.2 per cent. Oxygen given as on previous day. Pulse 86 before; 84 after; respiration 22 before and after. No change subjectively. Arterial saturation at end of oxygen 98.7 per cent.; venous saturation 88.9 per cent.; arterial carbon dioxid content, 50 volume per cent., unchanged by administration. No further oxygen was administered. Patient was operated on two days later, simple thoracotomy with insertion of catheter, and again ten days later, rib resection. He made a good recovery. Discharged Jan. 9, 1921, with very slight discharge from operative site.

In ths patient empyema was present for five days before oxygen was administered. Daily aspiration reduced the temperature, but failed to relieve the prostration. An arterial anoxemia was demonstrated for the two days preceding the administration, was completely removed by inhalation of oxygen for one-half hour, and continued absent on the following day. Beyond the slowing of the pulse and the deeper breathing no other clinical effects were observed. It cannot be said definitely that the single administration of oxygen caused the oxygen of the arterial blood to remain elevated. Actual changes in the lungs were perhaps the cause. However, the increased depth of respiration may have persisted and accomplished complete aeration of the lung. That a vicious circle of shallow breathing may itself cause anoxemia and be completely and permanently relieved by oxygen inhalation has been emphasized by Haldane and commented upon in the previous paper. This condition of affairs may well be present in weakened states following pneumonia, especially in the course of a disease where shallow breathing is encouraged by long-standing pleurisy. Subjectively, he felt no improvement during or after the administration.

Case 16 (Table 3).—L. N., white, female, housewife, age 53 years.

Diagnosis.—Bronchopneumonia; asthma.

History.—Attacks of tightness in chest, cough and sputum for thirty years. Three weeks before admission developed a head cold, one week later a cough, and six days before entry pains in right chest, prostration and dyspnea.

Physical Examination.—Temperature, 102 F.; pulse, 120; respiration, 35. Moderate dyspnea. Slight cyanosis of mucous membranes. Lungs contain sibilant and sonorous râles scattered throughout. Over right lower lobe posteriorly, increased voice and tactile fremitus present with fine crackling râles. Heart not enlarged; no murmurs. Blood culture sterile. Pneumococcus I in sputum. White blood cells 20,800; polymorphonuclears, 86 per cent. Blood Wassermann negative. Urine negative.

Course and Treatment.—Routine pneumonia treatment. On the first two days, the temperature oscillated between 100 and 102 F., and on the third day (and thereafter) it remained below 100.5 F.

January 17, 1921 (third day in hospital): Patient was quite comfortable and complained only of shortness of breath. Dyspnea was moderate. No cyanosis evident. Oxygen was administered through the mouthpiece for twenty minutes. She breathed comfortably throughout, using about 70 per cent. oxygen, and at

the end said the oxygen had a "soothing" effect. Saturation of the arterial blood directly before was 96.5 per cent.; directly after, 98 per cent.; arterial carbon dioxid content before, 50 volume per cent.; after, 50.5 volume per cent. Pulse, 96 before, 93 after. Respiratory rate, 28 before, 28 after. No change in color of skin or mucous membranes.

January 22: Temperature, pulse and respiration normal. Patient without symptoms.

This case is an example of a patient without anoxemia at the time of administration of oxygen. The arterial saturation was raised, the pulse slightly lowered, the resporatory rate unaltered. Subjectively, she was apparently much helped. The case itself was atypical in onset and course from the standpoint of a pneumococcus pneumonia.

CASE 17 (Table 3).—F. D., white, male, barber; age 23 years.

Diagnosis.—Septicemia; bronchopneumonia; erysipelas.

History.—Present illness began two weeks before admission with nervousness, vomiting, weakness and insomnia. For the week before admission he had fever, was at times irrational, and at times stuporous.

Physical Examination.—December 28, 1920. Temperature, 104 F.; pulse, 140; respiration, 40. Stupor and muscular twitchings. Respirations deep and rapid, rate 40. Heart not enlarged, no murmurs. Knee jerks active and equal. Lungs clear on day of admission. On following day, dulness, bronchial breathing, increased voice and tactile fremitus at left base posteriorly. Blood Wassermann negative. Two blood cultures negative. White blood cells, 11,000, polymorphonuclears, 70 per cent. Two Widals negative. Spinal fluid, normal pressure; negative for globulin; twenty-two cells, eighteen lymphocytes, four polymorphonuclear leukocytes. Sputum, pneumococcus type IV. Urine, sp. gr., from 1.020 to 1.030; slight trace of albumin.

Course and Treatment.—Typhoid precautions; forced fluids; soft solids.

Jan. 3, 1921: Temperature, 103 F.; pulse, 130; respiration, 40. Patient had been in hospital seven days without any essential change in condition. Respirations were rapid, regular, and deep, without grunting, and entirely through the nose. Lips were a dark deep red. No cyanosis of face or fingers. His hands moved restlessly and twitched at the bed clothes. Oxygen saturation of the arterial blood, 98.9 per cent., of the venous blood 82.3 per cent.; arterial carbon dioxid content, 42 volume per cent. Oxygen was administered through the mouthpiece for one-half hour, patient inhaling about 80 per cent. oxygen. He breathed deeply as before, but quietly and comfortably, eyes closed most of the time. At the end, there was a little increased pinkness under the eyelids. Pulse varied between 129 and 135 before oxygen, 126 and 129 during oxygen, 114 and 120 for the three hours following. Respiratory rate, 40 before and after.

January 4: Patient was stuporous, otherwise unchanged. Arterial saturation 93.9 per cent., venous saturation 77.1 per cent.; arterial carbon dioxid content, 42.4 volume per cent. Carbon dioxid dissociation curve showed an uncompensated acidosis. No further oxygen was administered. Sodium bicarbonate was given, correcting the acidosis and ameliorating his stupor and hyperpnea. Arterial saturation on the following day 97.7 per cent., venous saturation 85.2 per cent.; arterial carbon dioxid content, 44.5 volume per cent. Carbon dioxid dissociation curve showed a slight alkalosis. He failed to improve however and five days later, having developed a terminal erysipelas, died.

The clinical diagnosis was septicemia with metastatic bronchopneumonia. The arterial saturation was normal, the venous saturation above normal. (In several cases of acidosis of varying causes the

oxygen saturation of the venous blood has been found higher than normal and is probably explained by the hyperpnea.) Oxygen was easily and effectively given but without any definite changes in his condition. This was to be expected in the face of high normal values of oxygen saturation. The dyspnea and hyperpnea are partly accounted for by an acidosis, but since some dyspnea and hyperpnea were present even after this was corrected one must look further for a toxic factor, presumably acting on the respiratory center.

CASE 18 (Table 3).—E. A., white, male, machine finisher; 53 years. Admitted March 4, 1921.

Diagnosis.—Lobar pneumonia.

History.—Eight days before entry, he was seized with a severe chill and pain in right side. On the following day he developed cough and rusty sputum. Condition grew steadily worse and he became cyanotic.

Physical Examination.—March 4, 1921 (eighth day of disease): Temperature, from 102.5 to 105 F.; pulse, 128; respiration, 35. Stuporous, irrational, dyspneic. Low gurgling sounds during respiration. Finger-nails, a grayish dusky color, ears slightly cyanotic. Intermittent hiccough. Dulness, bronchial breathing, and many coarse moist râles over right upper and middle lobes, and left upper and left lower lobe. Heart slightly enlarged, without murmurs or irregularity. Pulse easily compressible, good volume, rate 128. Urine, sp. gr., from 1.010 to 1.020; occasional slight trace of albumin. Blood Wassermann, negative. White blood cells, 16,600; polymorphonuclears, 90 per cent. Sputum inoculation gave a pneumococcus type I.

Course and Treatment.—Routine pneumonia treatment. No digitalis.

March 4, 1921 (eighth day of disease): Arterial saturation, 76.8 per cent.; venous saturation, 71.5 per cent.; arterial carbon dioxid content, 49.1 volume per cent.; venous carbon dioxid content, 51.2 volume per cent. Oxygen was given through the Haldane apparatus, rate from 3 to 4 liters per minute, for two hours in the morning, three hours in the afternoon, and six hours in the night. Pulse was 130 before, 122 after oxygen had been given one and one-half hours. Respiration, 32 before, 28 after one and one-half hours. Cyanosis cleared. No further reduction in pulse or respiration occurred.

March 5 (ninth day of disease): Temperature, from 102 to 103.5 F.; pulse, 120; respiration, 35. Condition seemed definitely improved. No gurgling sounds during respiration. Oxygen was given for two hours in the morning, and blood taken for analysis at the end, while patient was still breathing through mask. Arterial saturation, 100 per cent.; venous saturation, 79.1 per cent.; arterial carbon dioxid content, 49.5 volume per cent. Pulse 120 before, 111 after. Respiration, 35 before; 36 after. Oxygen given for two hours in the afternoon, and six hours in the night.

March 6 (tenth day of disease): Temperature from 101 to 102.5 F.; pulse, 102; respiration, 28. General condition, little changed. Patient was still irrational, though less stuporous. Slight cyanotic tinge to finger-nails in the morning. (Had not had oxygen for one hour.) Oxygen was given for eight hours in the day and night, usually in one-hour periods.

March 7, (eleventh day of disease): Temperature, 98.6 F.; pulse, 90; respiration from 22 to 25. Crisis occurred during the night. Patient was still irrational. Hiccup continued. Lungs showed many coarse moist râles over both chests posteriorly. There was still a slight cyanotic tinge in the absence of oxygen. During the following five days, oxygen was given for one hour, three times a day, at the end of which time the finger-nails possessed no cyanosis in the absence of oxygen. Patient was still slightly irrational, but gradually

TABLE 3.—Effect of Oxygen Therapy on the Blood Gases in Twelve Cases of Pneumonia

Case No.	Diagnosis	Date	Oxygen Inhalation	Oxygen Content		Oxygen Saturation		Oxygen Capacity Vol. %	Hemoglobin Calculated from Oxygen Capacity	Carbon dioxid Content		Outcome	Remarks
				Arterial Vol. %	Venous Vol. %	Arterial %	Venous %			Arterial Vol. %	Venous Vol. %		
10	Lobar pneumonia; chronic pulmonary tuberculosis; pulmonary edema	1/31/21	No oxygen	15.69	10.29	77.2	50.2	20.30	100.9	49.5	53.1	R	Cyanosis +++
		2/ 1/21	2 hrs. after oxygen	15.72	12.43	75.9	60.1	20.74	112.0	62.8	67.0	..	Cyanosis +++
		2/ 2/21	12 min. after oxygen	13.89	11.92	62.3	53.5	22.30	120.4	60.4	60.2	..	Developed pulmonary edema; cyanosis ++++
		2/ 3/21	Oxygen day and night	17.02	16.22	82.2	78.4	20.75	112.1	66.7	70.0	..	Gurgling respiration absent; cyanosis +
11	Lobar pneumonia	11/24/20	Before oxygen	18.60	12.42	98.8	66.0	18.81	101.8	53.5	56.3	R	
			Oxygen for 30 min.	.....	14.08	....	74.6	(18.81)	(101.8)	....	57.0		
		11/25/20	Before oxygen	18.21	.....	90.8	....	20.10	108.5	52.9	....	..	Consolidation extended to L. L. L.
		11/26/20	Before oxygen	18.04	.....	99.7	....	18.10	97.9	61.0			
12	Lobar pneumonia;	2/28/21	Before oxygen	.....	13.53	....	63.5	21.35	115.2	....	51.7	R	Pulmonary edema; cyanosis ++++
	pulmonary edema	3/ 1/21	Oxygen for 10 hrs.	16.49	11.95	88.9	64.5	18.55	100.1	58.0	55.5	..	Cyanosis +
		3/ 3/21	Oxygen for 30 min.	17.65	.....	96.0	....	19.00	102.8	....	....	..	After crisis
13	Lobar pneumonia	1/ 5/21	No oxygen	19.64	.....	92.4	....	21.24	115.0	42.0	....	R	Cyanosis +
		1/ 6/21	Before oxygen	17.48	14.72	94.3	79.5	18.52	100.1	44.3	45.0	..	Cyanosis +
			Oxygen for 20 min.	18.14	.....	98.0	....	(18.52)	(100.1)	44.8	....	..	Cyanosis 0
		1/ 7/21	Before oxygen	15.76	.....	96.5	....	16.32	88.4	45.3	....	..	Cyanosis 0
		1/18/21	No oxygen	16.54	.....	96.5	....	17.14	.....	50.6	....	..	Patient well
14	Lobar pneumonia; empyema; chronic alcoholism	11/29/20	Before oxygen	.....	9.63	....	52.6	18.30	99.0	....	....	D	Cyanosis ++++
			Oxygen for 20 min.	.....	10.22	....	56.0	(18.30)	98.8	....	....	..	Cyanosis +++
		11/30/20	Before oxygen	14.74	10.88	74.4	54.8	19.85	107.2	47.0	46.4	..	Cyanosis ++++
		12/ 1/20	Before oxygen	.....	7.44	....	32.2	23.09	124.9	....	....	..	Cyanosis +++
		12/ 2/20	Oxygen for 45 min.	16.09	6.33	91.6	36.0	17.55	95.0	47.2	53.7	..	Cyanosis ++
		12/ 3/20	Before oxygen	.....	8.33	....	46.1	18.05	97.6	....	....	..	Cyanosis ++
		12/ 6/20	Before oxygen	18.98	11.83	92.7	57.8	20.43	110.5	40.6	40.2	..	Cyanosis +
			Oxygen for 20 min.	.....	11.85	....	58.0	(20.43)	(110.5)	....	50.0	..	Cyanosis +; day of death
15	Lobar pneumonia; empyema	12/ 7/20	No oxygen	15.04	.....	88.9	....	16.92	91.5	49.0	....	R	Empyema present before treatment
		12/ 8/20	Before oxygen	13.24	9.00	85.5	58.0	15.50	83.8	47.0			
			Oxygen for 20 min.	16.10	12.58	100.3*	81.2	(15.50)	(83.8)				
		12/ 9/20	Before oxygen	14.55	13.84	96.6	88.2	15.49	83.7	50.0	50.4		
			Oxygen for 20 min.	15.28	13.73	98.7	88.9	(15.49)	(83.7)	50.0	52.4		
16	Bronchopneumonia	1/17/21	Before oxygen	12.05	.....	96.5	....	12.5	67.6	50.0	....	R	No cyanosis
			Oxygen for 20 min.	12.24	.....	98.0	....	(12.5)	(67.6)	50.5	....	..	No cyanosis
17	Septicemia; bronchopneumonia	1/ 3/21	Before oxygen	22.56	18.73	98.9	82.3	22.80	123.0	42.0	42.5	D	
		1/ 4/21	Before oxygen	19.04	15.66	93.9	77.1	20.30	109.9	42.4	43.8		
		1/ 5/21	No oxygen	18.75	16.33	97.7	85.2	19.20	103.9	44.5	46.5		
18	Lobar pneumonia; pulmonary edema	3/ 4/21	Before oxygen	12.94	12.03	76.8	71.5	16.83	91.0	49.1	51.2	R	Pulmonary edema; cyanosis +++
		3/ 5/21	Oxygen for 13 hrs.	18.84	14.73	100.0†	79.1	18.65	100.9	49.5	....	..	Cyanosis 0
19	Lobar pneumonia; acute pulmonary tuberculosis	3/16/21	Before oxygen	15.44	13.88	87.5	78.6	17.65	95.4	40.4	41.2	R	Cyanosis +
20	Lobar pneumonia	1/28/21	Before oxygen	18.84	13.08	92.5	64.1	20.40	110.1	36.6	41.4	R	Cyanosis +
			2½ hrs. after oxygen	18.14	.....	89.1	....	20.39	110.0	41.3	....	..	Cyanosis +
		2/15/21	No oxygen	19.36	.....	96.2	....	20.14	108.9	55.0	....	..	Patient well
21	Lobar pneumonia	3/11/21	Before oxygen	12.94	.....	81.1	....	15.99	86.5	45.6	....	R	Cyanosis ++
		3/14/21	No oxygen	14.83	.....	88.5	....	16.80	90.8	48.1	....	..	24 hrs. after crisis; cyanosis +
22	Bronchopneumonia	12/11/20	Not treated	20.24	.....	91.9	....	22.3	120.2	37.8	....	D	CO_2 dissociation curve showed a CO_2 acidosis
23	Lobar pneumonia	12/13/20	Not treated	16.74	14.92	78.6	65.9	21.30	115.0	51.6	52.8	D	CO_2 dissociation curve showed a slight CO_2 acidosis
24	Chronic nephritis; uremia; bronchopneumonia; pulmonary edema	10/23/20	Not treated	24.34	10.63	83.7	36.6	29.10	157.0	35.4	44.8	D	

* The arterial content was 0.6 volume per cent. higher than the capacity. This probably represents an excess of oxygen in physical solution.
† The arterial content was 0.19 volume per cent. higher than the capacity, a difference within experimental error.

regained his normal mental state in the next four days. Lung signs largely cleared. He left the hospital twenty days after the crisis, feeling completely well.

This patient had a severe arterial (anoxic) anoxemia with a normal venous saturation. The diminished arterial saturation can be accounted for by the marked amount of edema that was present over the consolidated areas. The difference between the arterial and venous saturation was even less than normal, indicating presumably an efficient blood flow attempting to compensate for the diminished oxygen in the arterial blood. The administration of oxygen with the Haldane apparatus for thirteen out of twenty-six hours raised the arterial saturation to the normal, elevated slightly the venous saturation, and resulted in definite clinical improvement. For three days oxygen was administered from eight to eleven hours a day, at the end of which time patient had a crisis and thereby passed from an extremely critical condition to one of comparative safety. It seemed that the administration of oxygen in this very sick patient averted a fatal outcome by keeping him largely free from anoxemia for the three days preceding the crisis.

Case 19 (Table 3).—M. D., white, school girl; 18 years. Admitted March 11, 1921.

Diagnosis.—Lobar pneumonia; acute pulmonary tuberculosis.

History.—Chronic cough for 4 years. Pleurisy with effusion one year before entry. Six days before entry, headache and vomiting began, followed in next two days by cough, rusty sputum, and pain in right side.

Physical Examination.—March 11, 1921 (sixth day of disease): Temperature, 104 F.; pulse, 122; respiration, 40. Dyspneic grunting respiration. Moderate cyanosis of nails and mucous membranes. Signs of consolidation over left lower lobe, with few consonating râles. Heart without enlargement, irregularity, or murmurs. Pulse full and of good tension. Urine, sp. gr. from 1.013 to 1.028; slight trace of albumin. Blood Wassermann, negative. White blood cells, 19,000; polymorphonuclears, 78 per cent. Sputum, pneumococcus II and acid-fast bacilli. Blood culture sterile.

Course and Treatment.—Routine pneumonia treatment. Digitalis leaves, 1½ grains, twice a day from March 12 to March 21.

March 16, 1921 (eleventh day of disease): Temperature, 103.4 F.; pulse, 120; respiration, 35. Patient continued to be markedly prostrated. Signs of consolidation had spread to right lower lobe. Very few râles. Arterial saturation 87.5 per cent.; venous saturation, 78.6 per cent.; arterial carbon dioxid content, 40.4 volume per cent., venous carbon dioxid content, 41.2 volume per cent. Carbon dioxid dissociation curve showed no acidosis. Oxygen was given through mouthpiece for fifteen minutes, patient breathing about 40 per cent. oxygen. Slight cyanotic tinge to nails seemed less marked after oxygen. Pulse before, 120; after, 110; five minutes later, 112; fifteen minutes later, 108; forty-five minutes later, 116; one hour later, 120. Respiration from 34 to 36, unchanged throughout.

March 17 (twelfth day of disease): Temperature, 103.2 F.; pulse, 104; respiration, 34. Condition little changed. Oxygen given for twenty-five minutes. Pulse before, 104; after, from 96 to 100. Respiration 34, unchanged. Very slight cyanotic tinge in the nails seemed diminished after oxygen. On both occasions patient thought oxygen helped her a little by making her breathing easier.

Patient remained in the hospital twenty-two more days. During this time, temperature and pulse remained elevated, scattered areas of bronchial breathing and râles appeared throughout both chests, tubercle bacilli became numerous in the sputum, and she was finally transferred to a hospital for tuberculosis.

In this patient, a pneumococcus pneumonia apparently caused an acute flare-up of a chronic pulmonary tuberculosis. An arterial (anoxic) anoxemia was present with a normal venous saturation. Inhalation of oxygen resulted in slowing of the pulse and in a slight diminution of the cyanosis.

Case 20 (Table 3).—W. W., white, male, shipping clerk; 20 years. Admitted Jan. 26, 1921.

Diagnosis.—Lobar pneumonia.

History.—Five days before entry patient was seized with a sudden chill, followed the next day by cough, pain in right chest, fever, and diarrhea. For the last three days he has been mentally confused.

Physical Examination.—Jan. 26, 1921 (fifth day of disease): Temperature, 105 F.; pulse, 140; respiration, 35. Moderate dyspnea. Slight bluish tinge to finger-nails. Respiration was without expiratory grunt, not particularly shallow or rapid. Slight prostration. Dulness, bronchovesicular breathing, and crepitant râles at right upper lobe. Rest of chest clear. Heart without enlargement, irregularity or murmurs. Pulse of good volume and tension. Urine, sp. gr., from 1.009 to 1.024; occasional slight trace of albumin. White blood cells, 11,000; polymorphonuclears, 83 per cent.; three days later 25,100. Blood Wassermann, negative. Blood culture, pneumococcus type I. Sputum, pneumococcus type I.

Course and Treatment.—Routine pneumonia treatment. No serum therapy. No digitalis.

January 28 (seventh day of disease): Temperature 104 F.; pulse, 130; respiration, 45. Condition seemed unchanged. Arterial saturation, 92.5 per cent.; venous saturation, 64.1 per cent.; arterial carbon dioxid content, 36.6 volume per cent.; venous carbon dioxid content, 41.4 volume per cent. Carbon dioxid dissociation curve showed a distinct acidosis. No oxygen given.

January 29 (eighth day of disease): Temperature, 103.8 F.; pulse, 130; respiration, 40. Patient more distressed. Breathing was more shallow and dyspneic. Cyanosis of nails seemed unchanged. Oxygen was given through the mouthpiece for twenty minutes, patient breathing comfortably and using from 60 to 70 per cent. oxygen. Respiration became almost one-half as rapid and much deeper; color appeared to be unchanged. Respiration before, 42; after, 26; five minutes later, 40. Pulse before, from 120 to 124; after, 120; five minutes later, from 116 to 120. Subjectively he noticed no change. Arterial saturation two and one-half hours later, 89.1 per cent.; arterial carbon dioxid content, 41.3 volume per cent. That night the patient had a crisis.

February 15: Temperature, pulse and respiration normal. Patient well. Arterial saturation, 96.2 per cent. Carbon dioxid dissociation curve normal.

The single administration of oxygen for twenty minutes had no noticeable effect on the cyanosis or pulse. The breathing was markedly, though temporarily, slowed and deepened. Two and one-half hours later the arterial saturation was slightly less than the day before, indicating no lasting increase in the arterial oxygen and, together with

the lack of improvement in the cyanosis, suggesting that oxygen in this case did not further saturate the hemoglobin. Any effect it had was due to the temporary increase of the oxygen in physical solution in the blood.

CASE 21 (Table 3).—L. S., white, male, laborer; 50 years.

Diagnosis.—Lobar pneumonia; empyema.

History.—Twelve days before entry patient developed a chill, pain in right chest, cough and sputum. Fever and prostration continued unabated up to time of admission.

Physical Examination.—March 10, 1921 (twelfth day of disease): Temperature, 104 F.; pulse, 147; respiration, 50. Marked prostration and dyspnea. Respirations rapid and shallow, accompanied by expiratory grunt. Slight cyanosis of nail beds. Bronchial breathing and dulness over left lower lobe posteriorly, without râles. Heart without enlargement, irregularity, or murmurs. Pulse rapid, small volume. Urine, sp. gr., from 1.015 to 1.018 on ten examinations; occasional slight trace of albumin; frequent casts. Blood Wassermann, strongly positive. Blood culture, sterile. White blood cells 26,400; polymorphonuclears, 96 per cent. Sputum, pneumococcus type I.

Course and Treatment.—Routine pneumonia treatment. No serum therapy. Digitalis leaves, 1½ grains twice a day from March 12 to March 23.

March 11 (thirteenth day of disease): Temperature, 103 F.; pulse, 110; respiration, 50. Condition seemed unchanged. Arterial saturation 81.1 per cent.; arterial carbon dioxid content, 45.6 volume per cent. Carbon dioxid dissociation curve showed an uncompensated carbon dioxid acidosis.

March 12 (fourteenth day of disease): Temperature, 103 F.; pulse, 104; respiration, 46. Pulse slower, otherwise unchanged. Oxygen given through the mouthpiece for thirty minutes, patient breathing about 50 per cent. oxygen. Cyanosis of nails decreased but did not disappear. Pulse before, from 100 to 104; after, from 96 to 100. Respirations, from 46 to 48 before, from 46 to 48 after. No subjective changes. Temperature fell to normal that night.

March 14: Temperature, 99 F.; pulse, 90; respiration, 28. Slight cyanosis persisted. Arterial saturation, 88.5 per cent.; arterial carbon dioxid content, 48.1 volume per cent. Carbon dioxid dissociation curve showed a slight carbon dioxid acidosis. Three days later, temperature again rose and patient was subsequently operated on for empyema. He made a gradual recovery.

In this case, a single administration of oxygen was given. The cyanosis was decreased during the inhalation but did not wholly disappear. The pulse was at times slightly slowed during the administration. No other clinical effects were noted. The arterial anoxemia persisted in part even after the crisis.

DISCUSSION

There were ten patients with lobar pneumonia and two patients with bronchopneumonia treated by oxygen inhalation. All had an arterial anoxemia at some stage of the disease, except one of the cases of bronchopneumonia. (These cases were usually selected because of the presence of cyanosis, and do not therefore indicate the incidence of anoxemia in lobar pneumonia.) Of the ten patients with lobar pneumonia, there were eight in whom blood determinations were done in relation to oxygen therapy. The arterial saturation was increased

in all except one. In four it was raised to the normal level. In the remaining three, all of whom were very anoxemic and two of whom had pulmonary edema, the arterial saturation was notably increased by oxygen but did not reach normal limits. In the two cases of lobar pneumonia where the blood determinations did not have a definite relation to oxygen therapy, the cyanosis was decreased but did not seem entirely removed. In the two cases of bronchopneumonia, one showed a normal saturation of the arterial blood before the inhalation but showed a slight fall twenty-four hours later. The second, tested before and directly after the inhalation, showed an increase in arterial saturation. Thus, in the majority of the patients who suffered from anoxemia, it was possible to increase markedly the oxygen of the arterial blood. (Table 4 shows the degree of improvement.) In four of the ten, it was possible to raise the arterial saturation to the normal level. These facts have a distinct bearing on the cause and prognosis of cyanosis in pneumonia.

TABLE 4.—Degree of Relief of Anoxemia Following Oxygen Therapy

Complete Relief				Partial Relief				No Relief			
Case No.	Arterial Saturation		Outcome	Case No.	Arterial Saturation		Outcome	Case No.	Arterial Saturation		Outcome
	Before Oxygen, %	After Oxygen, %			Before Oxygen, %	After Oxygen, %			Before Oxygen, %	After Oxygen, %	
15	85.5	100.0	R	14	74.4	91.6	D	20	92.5	89.1	R
13	94.3	98.0	R	10	62.3	82.2	R				
18	76.8	100.0	R	21	81.1	*	R				
11	90.8	99.7	R	19	87.5	*	R				
				12	*	88.9	R				

* In these three cases, partial relief of anoxemia was shown by diminished cyanosis after oxygen.
R = recovered; D = died

It may first be said that cyanosis in pneumonia generally runs parallel to the degree of arterial unsaturation, as was pointed out by Stadie,[4] (That cyanosis of the nail beds is more frequent in pneumonia and lip cyanosis in cardiac disease was observed by Stadie, and has likewise been our experience. It seems worthy of emphasis that the patients who have a dark grayish or dusky gray color to the nails, in which the blue color is very slight, usually have a severe arterial anoxemia.) Lundsgaard[5] believes that the degree of cyanosis is dependent on the actual amount of reduced hemoglobin present in the capillary blood. Thus, patients who have a high hemoglobin will exhibit more cyanosis than patients with a low hemoglobin, even though the saturation of arterial and venous blood be the same. Slight

4. Stadie, W. C.: The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, J. Exper. M. **30**:215, 1919.
5. Lundsgaard, C.: Studies on Cyanosis, J. Exper. M. **30**:259, 1919.

cyanosis in cases of anemia becomes of graver significance than in the normal or plethoric individual. For the purpose of directly correllating the degree of cyanosis with the degree of anoxemia, the oxygen unsaturation in c.c. of oxygen per 100 c.c. of blood appears to be the best expression, since this gives the quantity of reduced hemoglobin. For the purpose, however, of estimating the severity of the disease, the oxygen saturation of the blood in per cent. is the best expression to use, for this in the arterial blood gives the diffusion pressure at which oxidation in the body takes place. As Barcroft [6] has shown, the organism is handicapped more by a lowering of the arterial saturation than by a corresponding diminution in oxygen content. In the venous blood, the saturation in per cent. gives an indication of blood flow that is not dependent on individual variations in hemoglobin, as are the oxygen unsaturation in volumes per cent. or oxygen consumption in volumes per cent.

In Stadie's cases of pneumonia, most of which were influenzal bronchopneumonia but which included seven cases of lobar pneumonia, the arterial oxygen saturation was considered a valuable prognostic sign, the cases with a markedly lowered arterial saturation being usually fatal. In this series, it was also evident that patients with a marked arterial anoxemia were the most desperately ill. A single determination is not, of course, of final significance, as the development of edema or an extension of consolidation alters the arterial saturation just as it changes the other features of the disease. In three of four extremely ill patients, all of whom had a severe arterial anoxemia and all of whom were treated with oxygen, three recovered. The clinical improvement took place as the oxygen in the arterial blood was elevated. In three untreated fatal cases, a marked arterial anoxemia was present in two. It is thus evident that a severe arterial anoxemia, if untreated, is generally followed by a fatal outcome. If the arterial anoxemia is effectively treated, the results in our cases would indicate a distinctly better prognosis.

Concerning the actual cause of cyanosis in pneumonia there is little agreement. Hoover,[7] stating that all cases of lobar pneumonia have a certain amount of cyanosis which he found proportionate to the area of lung involved, believed it due to an unrespired blood flow through the consolidated lung. According to Haldane,[8] in areas where complete con-

6. Barcroft, J.: Anoxemia, Lancet **1**:487, 1920.

7. Hoover, C. F.: Oxygen Therapy, J. A. M. A. **71**:880 (Sept. 14) 1918.

8. Haldane, J. S.: Recent Developments in the Therapeutical Use of Oxygen. Contributions to Medical and Biological Research Dedicated to Sir William Osler, **1**:550, 1919.

consolidation occurs the blood supply is commonly diverted. Gross [9] has demonstrated varying degrees of vascular obliteration corresponding to the stages of consolidation. It would appear that a certain amount of blood passed through the consolidated lung in red hepatization but practically none in gray hepatization. Meakins [10] concluded that the anoxemia of lobar pneumonia was the result of the rapid and shallow type of breathing. He found no relation between the degree of anoxemia and the extent of the consolidation.[11]

It is probable that these factors play a somewhat varying rôle. If one grants that lobar pneumonia may occur without cyanosis and without arterial anoxemia, and that has been our experience this year, it seems evident that in this type little or no unrespired blood flow passes through the consolidated lung. Similarly, in the cases in which oxygen inhalation raises the arterial saturation to the normal, it would appear that the consolidated area had little, if any, blood flow. Where the arterial anoxemia is only partially overcome by oxygen inhalation, the persisting cyanosis may be assumed to be due to a certain blood flow through the consolidated area, causing an admixture cyanosis. This condition seemed to be a factor in about half of our cases, but it was generally of slight degree, as the major portion of the anoxemia was usually relieved by oxygen therapy. In Meakins' two cases of lobar pneumonia reported in 1920,[12] and in two out of the three reported in 1921,[11] the arterial saturation was raised to the normal level by oxygen. Shallow breathing has only in a few cases been extreme enough to appear to be the chief cause of cyanosis. That it is an important factor and that it probably augments the anoxemia is definitely suggested by the work of Haldane, Meakins and Priestley.[13] In the concluding paper of this series, an example of an extreme type of shallow breathing occurring in lethargic encephalitis as the sole cause of a marked arterial anoxemia is described. In none of the cases of pneumonia did the shallow breathing approach the extent of these cases of lethargic encaphalitis. However, the mechanism of its production was clear, and indicates the probability of its occurrence in pneumonia in milder forms. There remains for explanation the major cause of the cyanosis.

9. Gross: Reconstruction of the Circulation of the Liver, Placenta, and Lung in Health and Disease, Canad. M. A. J. **9**:632, 1919.

10. Meakins, J. C.: Harmful Effects of Shallow Breathing, with Especial Reference to Pneumonia, Arch. Int. Med. **25**:1 (Jan.) 1920.

11. Meakins, J. C.: Observations on the Gases in Human Arterial Blood in Certain Pathological Pulmonary Conditions, and Their Treatment with Oxygen, J. Path. & Bacteriol. **24**:87, 1921.

12. Meakins, J. C.: Therapeutic Value of Oxygen in Pulmonary Lesions, Brit. M. J. **1**:324, 1920.

13. Haldane, J. S., Meakins, J. C. and Priestley, J. G.: The Effects of Shallow Breathing, J. Physiol. **52**:433, 1919.

From our results, the arterial anoxemia in pneumonia would appear to be largely related to the amount of local or widespread pulmonary edema. Swelling or edema of the alveolar walls and free fluid in the air spaces hinder gas exchange. This condition may occur adjacent to the hepatized area, in other parts of the lung, or widespread through both lungs. When generalized pulmonary edema is present, the hindrance to the mechanical passage of air is present in addition. The increased diffusion pressure of oxygen is able to overcome these resistances to the pulmonary exchange, as was demonstrated in the pulmonary complications of cardiac insufficiency. The fact that the arterial anoxemia is in large part overcome by oxygen administration supports this conception.

Hoover [7] has himself emphasized the importance of moisture in the lungs as a cause of cyanosis, although he did not believe it to be the usual cause in pneumonia. In edema of the lungs from gas poisoning or cardiac failure, or where moisture was present apart from the consolidation in pneumonia, oxygen therapy relieved the cyanosis but not the air-hunger. This he attributed to an increased carbon dioxid content of the aortic blood that resulted from the disturbance in respiratory exchange caused by foam or edema in the bronchial tree. This theory of carbon dioxid retention has recently received confirming evidence from Means and his collaborators [14] in pneumonia and Peters and Barr [15] in cardiac decompensation. Carbon dioxid dissociation curves have shown that in both these conditions there may be a carbon dioxid retention in the arterial blood of the extent to cause an actual change in p_H.

Concerning the dyspnea of lobar pneumonia, it may be said that anoxemia plays but a limited rôle. There was no constant relief of respiratory distress after oxygen therapy. Breathlessness would seem to be more closely related to a faulty pulmonary ventilation that was insufficient to get rid of carbon dioxid rather than insufficient to acquire oxygen. The alkali reserve was within normal limits, except in a few cases where it was only slightly lowered. The carbon dioxid content of arterial and venous blood was usually a little increased by oxygen therapy, but at times unaffected. These relationships will be discussed fully in a paper in which carbon dioxid dissociation curves in pneumonia are presented. In several tested cases, the blood bicarbonate

14. Means, J. H., Bock, A. V., and Woodwell, M. W.: Studies of Acid-base equilibrium in Disease from the Point of View of Blood Gases, J. Exper. M. **33**:201, 1921. Barach, A. L.; Woodwell, M. N., and Means, J. H.: The Reaction and Available Blood Alkali in Pneumonia. To be published.

15. Peters, J. P., and Barr, D. P.: The Carbon Dioxid Absorption Curve and the Carbon Dioxid Tension of the Blood in Cardiac Dyspnea, J. Biol. Chem. **45**:559, 1921.

showed a definite elevation as convalescence was reached. This fact and its bearing on the administration of alkali will be discussed in another paper.[16]

A fact brought out in connection with the inhalation of oxygen is the increase in the amount of circulating hemoglobin under varying conditions of anoxemia and its decrease after relief of the anoxemia. This relationship was more constant in the cardiac than in the pneumonia cases, although exceptions were common to both groups. The effect of oxygen want in increasing the number of red blood cells and hemoglobin in peripheral blood has long been known and is familiarly manifested in patients with congenital heart disease and in people who live at high altitudes. In the Pike's Peak expedition, Miss Fitzgerald[17] found that the increase in hemoglobin was proportionate to the increase in altitude, that is to say, the anoxemia. In the patients with chronic gas poisoning suffering from anoxemia, Barcroft[18] found a noteworthy fall in the red blood cells and hemoglobin after they had lived in an oxygen chamber five days. An insufficient oxygen supply has been shown to cause a definite increase in hemoglobin in one hour.[19] In one of our cases (Case 10), a fall in arterial saturation from 75 to 62 per cent. in one day resulted in an increase in oxygen capacity (representing the hemoglobin) from 20.7 to 22.3 volume per cent. On the following day, the inhalation of oxygen raised the arterial saturation to 82 per cent., and the oxygen capacity dropped to 20.7 volume per cent. again. In another case (Case 8), the inhalation of oxygen raised the arterial saturation to the normal in two hours and was accompanied by a decrease in capacity from 21.5 to 20.6 volume per cent.

This effect of oxygen want on the amount of circulating hemoglobin is emphasized particularly because the variations in the oxygen capacities of Stadie's cases[4] of pneumonia has been made the reason for criticism and for an assumption by Meakins[11] of inaccuracies in the Van Slyke methods. When Stadie's cases are examined, it is found that the majority of them show this fundamental mechanism. In his most marked case (Case 35) a severe arterial anoxemia gradually diminished as the patient recovered, and the oxygen capacity correspondingly diminished from 19.1 to 14.9 volume per cent. The

16. Means, J. H., and Barach, A. L.: Remarks on the Symptomatic Treatment of Pneumonia. Read at the Association of American Physicians, May 10, 1921.

17. Fitzgerald: Quoted from Haldane, J. S., Organism and Environment, 1917, p. 52.

18. Barcroft, J., Hunt, G. H., Dufton, D.: The Treatment of Chronic Cases of Gas Poisoning by Oxygen Administration in Chambers, Quart. J. M. **13**:179, 1920.

19. Gregg, H. W., Lutz, B. R., Schneider, E. C.: The Changes in the Content of Hemoglobin and Erythrocytes of the Blood in Man During Short Exposures to Low Oxygen. Am. J. Physiol. **1**:216, 1919.

average oxygen capacity of his nonfatal cases, characterized by little cyanosis, was 20 volume per cent., whereas the average of the fatal cases who uniformly had a marked cyanosis was 23 volume per cent. The nonfatal cases showed a decrease in oxygen capacity as they recovered and as they became free from oxygen want. In the cases of cardiac decompensation of Lundsgaard [20] this tendency can also be observed. A striking case (Case 3) showed a fall in capacity from 22.5 to 17.5 volume per cent. as compensation was regained and cyanosis disappeared. Cunningham [21] observed a patient with edema of the lungs at the height of the attack and when he was normal, and the oxygen capacities were, respectively, 25 and 19 volume per cent. Underhill and Ringer [22] studied cases of influenzal bronchopneumonia and found variations in hemoglobin from day to day, as high as from 20 to 30 per cent. Here, also, the hemoglobin increased as the patients became worse and decreased as they improved. This general relationship of an increase in hemoglobin to oxygen want is by no means constant in clinical disease, but it must be remembered that there are a multiplicity of factors that govern the amount of hemoglobin circulating in the blood. Schneider and Havens [23] found an increase in hemoglobin due to physical exertion, abdominal massage and pressure, injection of adrenalin, and during athletic training. Changes in the blood volume result inevitably in changes in hemoglobin, and Buckman [24] has demonstrated that such changes occur in pneumonia, the plasma volume being decreased during the course of the disease and returning to normal during convalescence. Variations in hemoglobin corresponding to the different periods of the day have been demonstrated, and, according to Dryer, Bazett and Pierce,[25] may reach as high as 30 per cent., while 10 per cent. changes are of more or less common occurrence. In consideration of these facts, it would appear that the occurrence in pneumonia of a changing oxygen capacity offers no basis for the assumption of inaccuracies in method but seems rather to demonstrate a fundamental physiological mechanism.

The venous saturation was determined in ten cases of lobar pneumonia and two cases of bronchopneumonia. A true stagnant anoxemia

20. Lundsgaard, C.: Studies of Oxygen in the Venous Blood. Determinations on Five Patients with Uncompensated Circulatory Disturbances. J. Exper. M. **27**:228, 1918.

21. Cunningham, D.: Quoted from Bock, A. V., Constancy of the Plasma Volume in Disease. Arch. Int. Med. **27**:83 (Jan.) 1921.

22. Underhill, F. P., and Ringer, M.: Blood Concentration Changes in Influenza with Suggestions for Treatment. J. A. M. A. **75**:1531 (Dec. 4) 1920.

23. Schneider, E. C., and Havens, L. C.: Changes in the Blood After Muscular Exertion and During Training. Am. J. Physiol. **36**:239, 1915.

24. Buckman, Thomas E.: Personal communication. To be published.

25. Dreyer, G., Bazett, H. C., Pierce, H. F.: Diurnal Variations in the Hemoglobin Content of the Blood. Lancet **1**:588, 1920.

was shown in one case of lobar pneumonia; in four others a relative lowering of the venous saturation occurred, due to the diminution of the arterial saturation. One of the cases of bronchopenumonia had a true stagnant anoxemia a short time before death. In influenzal bronchopneumonia Harrop [26] found the venous unsaturation normal up to the time of death. As discussed in the previous paper, a venous saturation below 65 per cent. does not indicate an impaired circulation unless the arterial saturation is normal. The normal difference between arterial and venous saturation, or coefficient of utilization, being between 20 and 30 per cent., and the results in this series lying for the most part within this range, would indicate a normal or increased blood flow in uncomplicated pneumonia.

In seven of the above cases, the venous blood was tested in relation to oxygen therapy. The venous saturation was increased in four, in three of which the rise was somewhat greater than could be accounted for by the arterial elevation, suggesting a temporarily increased blood flow. One of the most constant objective changes due to oxygen therapy was the slowing of the pulse, which apparently allowed the blood flow to be maintained at less effort from the heart.

Attention might be called to the similarity between the symptoms and signs of experimental anoxemia and anoxemia as it occurs in clinical disease. The elevated pulse, irrational states and delirium, cyanosis, rapid shallow or periodic breathing are common to patients with pneumonia or heart disease, as they are to individuals who have been experimentally deprived of oxygen. These harmful effects of anoxemia are, in the main, capable of relief or prevention. The patient is thus in better condition to withstand the other factors in the disease. When acute oxygen want supervenes, as in the development of pulmonary edema, a fatal outcome may be averted by overcoming the anoxemia. The patient is then in no sense cured, but he is given a renewed opportunity to cope with the remainder of the disease. If he can be tided over to the period of the crisis he has the chance of a swift decline in all his symptoms that would otherwise be lost to him. The effect of a single inhalation of oxygen in raising the arterial saturation is in the main temporary, although there is evidence that in cases in which shallow breathing is pronounced it may be more permanently elevated. Prolonged administration or frequently repeated administration can, however, keep the patient free from anoxemia most of the time, and has been attended by a diminution in the signs of lung edema As Haldane [27] has observed: "It may be argued that such measures as the administration of oxygen are

26. Harrop, G. A.: Behavior of the Blood Towards Oxygen in Influenzal Infections, Bull. Johns Hopkins Hosp. **30**:10, 1919.

27. Haldane, J. S.: The Therapeutic Administration of Oxygen, Brit. M. J. **1**:182, 1917.

at the best only palliative and of no real use, since they do not remove the cause of the pathological condition. As a physiologist, I cannot for a moment agree with this reasoning. The living body is no machine, but an organism constantly tending to maintain or revert to the normal, and the respite offered by such measures as the temporary administration of oxygen is not wasted but utilized for recuperation."

To combat anoxemia, oxygen must be given effectively. The Haldane apparatus is effective and convenient, if the patient can be made to bear the mask. The simple mouthpiece rebreathing method we have found effective and productive of minimal discomfort to the patient. The oxygen bed tent described by Leonard Hill[28] would appear to be very efficient and certainly merits further trial.

SUMMARY

1. There have been observed in all eleven patients with lobar pneumonia, each of whom had an arterial anoxemia at some stage of the disease, and four patients with bronchopneumonia, two of whom had an arterial anoxemia.

2. Ten patients with lobar pneumonia were treated by the inhalation of oxygen. In eight, the blood gas determinations were done before and after oxygen therapy. Of these, the arterial oxygen saturation was increased in all except one. In four, it was raised to the normal level.

3. Two patients with bronchopneumonia who had no arterial anoxemia were treated with oxygen. In one, the arterial saturation was shown to be increased directly after the inhalation. In the second, analysis twenty-four hours later showed a slight fall in arterial saturation.

4. A true stagnant anoxemia was demonstrated in one of ten cases of lobar pneumonia. In four other cases there was a relative lowering of the venous saturation due to the diminution of arterial oxygen. The difference between the arterial and venous saturation was generally normal or less than normal, indicating that a normal or increased blood flow is usually present in uncomplicated pneumonia.

5. The most consistent changes in the clinical condition of the patient were the clearing of the cyanosis and slowing of the pulse. The respiratory rate was sometimes slowed; the mental condition of the patient was frequently improved; the dyspnea was not usually relieved.

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28. Hill, L.: A Simple Oxygen Bed Tent and Its Use to a Case of Oedema and Chronic Ulcer of the Leg. J. Physiol. **50**: (May 24) 1921; Proc Physiol. Soc., p. 20.

6. Oxygen inhalation for one-half hour was sufficient in the mild or moderate cases of anoxemia to elevate the arterial saturation and cause clinical improvement. In the severe cases, one to two hours was necessary. The effect of a single administration was, in the main, temporary. The effect of repeated and prolonged administration produced persistent beneficial changes in the oxygen saturation of the blood, the pulse, breathing, color, comfort, and mental condition of the patient.

7. In three patients in whom a condition of acute oxygen want followed the development of pulmonary edema, the prolonged administration of oxygen resulted in striking clinical improvement, and seemed to avert a fatal outcome.

8. It is believed that oxygen therapy has a rational rôle in the treatment of pneumonia.

9. A convenient effective method of giving oxygen has been developed which does not cause discomfort to the patient.[29]

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29. The method of administering oxygen is described in Paper I of this series. The apparatus, with a few recent additions, can be secured from Mr. Warren E. Collins, 584 Huntington Avenue, Boston.

STUDIES IN OXYGEN THERAPY

III. IN AN EXTREME TYPE OF SHALLOW BREATHING OCCURRING IN LETHARGIC ENCEPHALITIS *

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The effects of oxygen inhalation on types of anoxemia frequently present in clinical disease, as those associated with cardiac insufficiency and pneumonia, have been described in Papers I and II of this series. The terminal development in two cases of lethargic encephalitis of a rare type of shallow breathing resulted in sudden extreme arterial anoxemia and carbon dioxid retention in arterial and venous blood. The effects of oxygen inhalation on the blood gases and on the clinical signs are reported in this paper.

REPORT OF CASES

CASE 25 (Table 2).—M. S., white, male, auto repairer; age, 25 years.

Diagnosis.—Lethargic encephalitis.

History.—Two weeks before entry, patient had right temporal headache. This was followed by pains in both arms and across the abdomen. During the three days prior to admission he developed fever, insomnia, blurring of vision and dropping of left eyelid.

Physical Examination.—Jan. 8, 1921: Temperature, 101 F.; pulse, 115; respiration, 25. Slight ptosis of both eyes, diplopia, weakness of left internal rectus muscle. Lungs clear and resonant. Heart not enlarged, no murmurs. Reflexes not abnormal. Urine negative. White blood cells, 11,100; polymorphonuclears, 79 per cent. Lumbar puncture revealed clear fluid under increased pressure; cells, 44; polymorphonuclears 14 and mononuclears 30; alcohol positive, ammonium sulphate negative, Wassermann negative.

Course and Treatment.—Jan. 10, 1921. At 1 a. m. he became suddenly dyspneic and cyanotic; temperature rose to 103 F.; pulse to 140; respiration to 48. At 10 a. m. he was comatose, deep and superficial reflexes could not be obtained, neck was stiff, the extremities were limp and flaccid. No Kernig was present, no Babinski or ankle clonus. Lungs clear and resonant throughout. He breathed in a rapid jerky manner; at each inspiration the upper abdomen underwent a double convulsive contraction with a simultaneous twitching of the neck muscles but without any movement of the intercostal muscles during either phase of respiration. His face was of a dusky grayish color, the lips deeply cyanotic, the nail-beds a light blue color. Oxygen had been administered during the night through a funnel held close to the nose, without alleviation of the cyanosis in any degree. The mask of the rebreathing apparatus was applied with a valve adjustment, giving about an 80 per cent. oxygen

* From the Medical Service of the Massachusetts General Hospital. This paper is No. 17 of a series of studies of the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

* The expense of this work was, in part, defrayed by a grant from the Proctor Fund of Harvard University for the study of chronic diseases.

mixture. It was then noticed that the rebreathing bag barely moved, and that an extreme type of shallow breathing was the cause of the cyanosis. This was in marked contrast to the convulsive movements of the upper abdomen, which suggested moderately deep breathing. At the end of five minutes a slight diminution of the cyanosis became noticeable; at the end of ten minutes it was strikingly diminished; after twenty-five minutes there was no cyanosis of face, fingers or mucous membranes, the nails were pink, the ears a rosy red, the lips free from any blueness. At the same time, the respiratory rate decreased from 45 to 34 and the pulse from 141 to 105 and later to 98. The extreme shallow character of the respiration persisted unchanged, but the spasmodic movements of the diaphragm had largely disappeared. The neck was no longer stiff. All the reflexes persisted absent.

TABLE 1.—Effect of Oxygen Inhalation on Pulse, Respiration and Cyanosis in Extreme Shallow Breathing in Case 25

Time	Pulse	Respiration	Cyanosis
10:25 Before oxygen	141	45	++++
10:35 During oxygen	132	..	++
10:45 During oxygen	120	..	+
10:55 During oxygen	105	38	0
11:00 During oxygen	98	..	0
11:20 During oxygen	112	40	0
11:28 Oxygen stopped for 3 min.	126	..	++
11:33 During oxygen	114	34	+
11:38 During oxygen	114	..	0
11:43 Oxygen stopped for 5 min.	141	..	+++
11:55 During oxygen	132	44	++
12:02 p. m. During oxygen	126	40	+
12:09 During oxygen	123	..	+
12:26 During oxygen	124	40	+
12:34 During oxygen	129	42	++
12:53 During oxygen	126	..	++
12:56 During oxygen	126	..	++
1:00 During oxygen	140	39	++
1:05 During oxygen	129	..	++
1:10 During oxygen	...	39	++
1:16 During oxygen	120	..	++
1:23 During oxygen	124	40	++
1:35 During oxygen	128	..	++
1:45 During oxygen	140	40	+++
2:00 During oxygen	140	..	+++
2:20 During oxygen	140	40	+++

The inhalation of oxygen relieved the arterial anoxemia and resulted in a striking slowing of the pulse. The withdrawal of oxygen caused a simultaneous increase in the anoxemia and in the pulse rate. The arterial oxygen saturation was raised from 60.7 to 84.5 per cent. in forty-five minutes. The arterial carbon dioxid content in that time mounted from 64.2 volume per cent. to 88.4 volume per cent., indicating a steadily increasing carbonic acidosis. Failure of the circulation finally occurred, and accounted for the reappearance of the cyanosis.

The oxygen saturation of the arterial blood before the inhalation was 60.7 per cent.; the venous saturation was 46.4 per cent.; the arterial carbon dioxid content, 64.2 volume per cent.; the venous carbon dioxid content, 68.4 volume per cent. After oxygen had been given for forty-five minutes, the arterial saturation was 84.5 per cent.; the arterial carbon dioxid content, 88.4 volume per cent.; after fifty-five minutes the venous saturation was 87.9 per cent.; the venous carbon dioxid content, 88.6 volume per cent. When oxygen had been given for one hour it was stopped for three minutes. The cyanosis returned and the pulse began to climb, reaching 126. Oxygen was recommenced and given for five minutes, when the tank gave out. Pulse was then 114. It was five minutes before another tank had been secured, and in the meantime pulse rose to 141, respiration to 44, color changed to deep cyanosis of lips and finger nails. Oxygen was begun again but with less relief than formerly. Pulse slowed to 126 after the first hour and then gradually became elevated and feeble. Cyanosis increased moderately as circulation began to fail. After three more hours oxygen was stopped and patient died three minutes later in deep cyanosis. (See Table 1 for effect on pulse and respiratory rates.)

Case 26 (Table 2).—E. D., white, housewife; age, 23 years.

Diagnosis.—Lethargic encephalitis.

History.—Ten days before entry an aching pain appeared behind right ear. Headache persisted up to time of admission, confined to right temporal region and variable in severity. She developed pains in chin, neck and shoulder blades. When the pains in the shoulders occurred respiration became very rapid and jerky (husband's statement). For seven days blurred vision and diplopia were present. Felt sleepy but found it difficult to go to sleep.

Physical Examination.—Jan. 23, 1921: Temperature, 101 F.; pulse, 130; respiration, 40. Double ptosis, double facial paralysis. Fields of vision limited in both eyes. Right leg twitches involuntarily. Knee-jerks not obtained. No other abnormal reflexes. Heart and lungs not abnormal. Urine negative. White blood cells, 11,200; polymorphonuclears, 75 per cent. Blood Wassermann, negative. Nonprotein nitrogen 53.1 mg. per 100 c.c. Spinal fluid under increased pressure, 20 cells, 14 polymorphonuclears and 6 lymphocytes. Alcohol negative. Ammonium sulphate negative. Culture sterile. Wassermann negative.

TABLE 2.—Effect of Oxygen Inhalation on the Blood Gases in Extreme Shallow Respiration Occurring in Two Cases of Lethargic Encephalitis

Case No.	Diagnosis	Date, 1921	Oxygen Inhalation	Oxygen Content		Oxygen Saturation		Oxygen Capacity Vol. %	Hemoglobin Calculated from Oxygen Capacity	Carbon Dioxid Content	
				Arterial Vol. %	Venous Vol. %	Arterial %	Venous %			Arterial Vol. %	Venous Vol. %
25	Lethargic encephalitis	1/10	Before oxygen	14.74	11.29	60.7	46.4	24.30	131.2	64.2	68.4*
			Oxygen for 1 hr. 30 min.	20.29	.....	84.5	....	(24.30)	(131.2)	88.4†	
			Oxygen for 1 hr. 40 min.	.....	21.37	....	87.9	(24.30)	.....	....	88.6†
26	Lethargic encephalitis	1/25	Before oxygen	13.70	.....	64.5	....	21.31	115.0	51.0	
			Oxygen for 45 min.	17.44	.. .	82.0	....	(21.31)	(115.0)	62.0	

The oxygen saturation of the arterial and venous blood was raised. The carbon dioxid content of the blood steadily increased.

* Carbon dioxid dissociation curve showed an acidosis.

† This value is approximate because the combined gases were above the calibrated portion of the pipet.

Course and Treatment.—Jan. 25, 1921. Temperature, 102.5 F.; pulse, 140; respiration, 45. At 7:30 a. m., patient went into coma, became cyanotic and breathed in a rapid, jerky manner. Lips and ears showed moderate cyanosis, the finger nails very marked cyanosis. Moist râles present at right base. Pulse of poor quality, rate 141. Oxygen was given through a mask with valve attachment providing about an 80 per cent. oxygen mixture for three hours. The first effect noticeable was a definite slowing of the pulse. In three minutes it slowed from 141 to 132; in fifteen minutes it had attained its maximal slowing, 114; after this the pulse rose and showed only slight or temporary periods of slowing. The cyanosis began to diminish in five minutes and became progressively less for twenty minutes; at that time there was just a slight bluish tinge to the nail beds which never wholly disappeared. Respirations continued very shallow and rapid, rate from 45 to 50. The cyanosis remained minimal for the first hour, increased in the second hour and was marked in the third hour. Whenever the oxygen was removed she became darkly cyanotic. (The persistence of the cyanosis in the presence of a rich oxygen mixture seemed due to the exceptional shallowness of the respiration and the stagnant circulation.) After three hours' oxygen the inhalation was

stopped and the patient died two minutes later. Ten minutes previous, 25 gm. sodium bicarbonate were given intravenously without effect.

The arterial oxygen saturation before the inhalation was 64.5 per cent.; after forty-five minutes, 82 per cent. Arterial carbon dioxid content before was 51 volume per cent.; after, 62 volume per cent. The carbon dioxid dissociation curve before oxygen showed a marked uncompensated carbon dioxid acidosis, p_H 7.22.

In both these cases the soda-lime was tested before and after using and found perfect for absorption of carbon dioxid.

In these two cases shallow breathing was the direct cause of a very marked arterial anoxemia. Because of the convulsive movements of the diaphragm the extreme shallowness of the respiration was not actually appreciated until the mask was applied, when it was noticed that the rebreathing bag barely moved. Interpretation of this unique phenomenon in lethargic encephalitis cannot be made with certainty as necropsies were not obtained. It seems probable, however, that the respiratory center in the medulla became involved in the inflammatory process, since lesions in the bulb are quite common in this disease.

Shallow breathing has been shown to be a cause of anoxemia by producing uneven ventilation of the lungs, and consequently incomplete oxygenation of the blood.[1] This is based on the conception of Keith [2] that expansion of the lungs takes place in a manner resembling the opening of a Japanese fan, the peripheral portions expanding first and the root region last. In these cases the total ventilation itself was so small that it was the air in the trachea and bronchi that became chiefly renewed and the alveolar air only secondarily changed.

The effects on the blood gases were first, a marked arterial anoxemia, and secondly, a retention of carbon dioxid in the arterial and venous blood. Oxygen therapy was able to increase greatly the arterial and venous oxygen saturation, but was powerless against the steady accumulation of carbon dioxid. In one case a carbon dioxid dissociation curve, done before oxygen was given, showed an uncompensated carbon dioxid acidosis, P_H 7.22.

In the beginning, the circulation was strikingly improved as a result of the relief of the anoxemia. (Table 1 shows the parallel effect on the pulse and cyanosis of the inhalation of oxygen.) The subsequent failure of the circulation seemed dependent on the increasing carbon dioxid retention in the blood, which showed no disposition to decrease since the shallowness of respiration itself persisted. The final cyanosis was thus of stagnant origin.

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1. Haldane, J. S.: Meakins, J. C., and Priestley, J. G.: The Effects of Shallow Breathing, J. Physiol. **52**:433, 1919.

2. Keith, A.: Quoted from Haldane, J. S.; Meakins, J. C., and Priestley, J. G.: The Effect of Shallow Breathing, J. Physiol. **52**:449, 1919.

SUMMARY

1. In two patients with lethargic encephalitis the development of an extreme type of shallow breathing was attended with deep cyanosis and coma. The arterial blood was markedly deficient in oxygen and contained an excess of carbon dioxid.

2. Inhalation of oxygen greatly relieved the arterial anoxemia but was without effect on the steady accumulation of carbon dioxid. An uncompensated carbon dioxid acidosis, p_H 7.22, was demonstrated in one case by a carbon dioxid dissociation curve.

3. The circulation was strikingly improved in the beginning as a result of the relief of the anoxemia. Later, progressive cardiac failure occurred, apparently related to the carbon dioxid retention.

4. It is evident that shallow respiration, if extreme, interferes not only with oxygen absorption but with carbon dioxid elimination.

5. It seems probable that a terminal involvement of the respiratory center in lethargic encephalitis is at times the cause of death.

THE TOTAL NONPROTEIN NITROGEN CONSTITUENTS OF THE BLOOD IN CHRONIC NEPHRITIS WITH HYPERTENSION*

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During the course of investigations regarding the presence and amount in the blood of various nitrogenous waste products usually excreted by the kidneys in patients with essential arterial hypertension but without nephritis, similar studies were made on eighty-eight patients with chronic nephritis and hypertension or with myocardial decompensation. Although similar studies have been reported by others, it is believed the results presented here will be of interest and afford suitable control to those previously reported.[1]

The patients studied are divided into three groups. All had arterial hypertension. Group I includes the patients with uremia; Group II those with a moderate increase in the various nonprotein nitrogen constituents of the blood, and Group III those with a slight increase.

Table 1 includes the maximum, minimum and average values for the urea, total nonprotein nitrogen, uric acid and creatinin of the blood for each of the three groups.

There are thirteen patients in Grouup I, all with a marked retention of nonprotein nitrogen compounds in the blood and all eventually died of uremia. Albumin was present in the urine of every patient and casts were present in all but two. Before the onset of uremia, there was a progressive increase in the amount of waste nitrogen retained in the blood with the progress of the disease. Nine patients were studied before and after coma supervened. As a rule, with the appearance of coma the various nitrogenous extractives of the blood were present in higher concentration than before. The unconsciousness lasted from two days to two weeks before death, and as it deepened there was an increase in the amount of the nonprotein nitrogen constituents of the blood. With two patients there was a terminal acidosis, as determined by the depression of the alkali reserve.

The ages in this group varied from 27 to 80 and averaged 45.2 years; the maximum systolic blood pressure varied from 176 to 272 mm., the diastolic from 75 to 170 mm.; the phenolsulphonephthalein test of renal function from a trace to 30 per cent., average 10.2 per

*From the Pathological Laboratory, St. Luke's Hospital; aided by the Seymour Coman Fund.

1. Arch. Int. Med. **27**:748 (June) 1921.

cent. in two hours. The Wassermann reaction of the blood for syphilis was positive in one patient and negative in nine patients; in three it was not learned.

There was no relationship between the height of the blood pressure and the degree of nitrogen retention in the blood nor was there any constant relationship between any of the symptoms and the amount of the nonprotein nitrogen in the blood. In general, the largest amount of uric acid was found in the blood of those patients with most marked cardiac decompensation or the retention of uric acid was most marked with the development of the decompensation.

Ophthalmoscopic examination of four patients revealed a hemorrhagic retinitis in two, and a chronic nephritis retinitis in two, one of whom had retinal hemorrhages. All thirteen patients of this group died.

The duration of life after blood was taken for chemical examination varied from two days to seven months, the average being fifty-eight days. The time limit in prognosis could not be foretold accurately by chemical examination of the blood, but generally the higher values for

TABLE 1.—NONPROTEIN NITROGEN CONSTITUENTS IN ONE MG. PER 100 C.C. OF BLOOD

	Uren N			Total N-P-N			Uric Acid			Creatinin		
Group	Maximum	Minimum	Average	Maximum	Minimum	Average	Maximum	Minimum	Average	Maximum	Minimum	Average
I	259.8	61.8	108.7	287.6	83.8	146.3	22.6	5.4	11.2	29.5	4.2	11.7
II	69.0	30.3	39.3	101.0	45.4	61.8	9.2	4.9	6.2	11.9	1.6	2.9
III	29.9	17.8	22.9	57.3	28.6	43.2	15.6	1.5	5.3	4.0	1.2	2.2

creatinin (average 17.6 mg.) were obtained in patients living only a short time (average twenty-six days). One patient, however, lived four months after a blood creatinin of 20.4 mg. per 100 c.c. had been obtained.

Postmorten examination of the bodies of two patients revealed a marked chronic diffuse nephritis with secondarily contracted kidneys, both with marked hypertrophy of the heart and a moderate degree of sclerosis of the aorta and larger arteries. Therefore, from chemical, functional and anatomic evidence coincident with clinical experience these thirteen patients with hypertension had chronic nephritis and died of uremia.

Included in Group II are thirty-six patients with a moderate degree of nitrogen retention in the blood. Their ages varied from 30 to 70, and averaged 52.4 years. The disease in five of these was diagnosed clinically as myocardial degeneration or myocarditis [2] with cardiac

2. This diagnosis of "myocarditis" is an error, since the alterations microscopically are edema and passive hyperemia without cellular exudate.

decompensation. Only two patients had neither albumin nor casts in the urine.

The systolic blood pressure ranged from 160 to 284 mm., the diastolic from 70 to 180 mm. mercury; the phenolsulphonephthalein test from 2 to 60 per cent. for the two hour period.

The Wassermann test for syphilis on the blood was positive in four patients and negative in twenty-three, but four of these gave a history of syphilis.

Dyspnea, headache and nocturia were the most prominent symptoms. Headache, nausea and vomiting were the symptoms most commonly associated with higher values for retained nitrogen, but this relationship was not constant. Headache, nausea and vomiting were much more common in this group than in Group III where the increase in the various nonprotein nitrogen substances is slight.

Ophthalmoscopic examination of twelve patients revealed a marked hemorrhagic retinitis in five, a chronic degenerative retinitis in seven with retinal hemorrhages in three, marked venous engorgement and arteriosclerotic changes in one each. The patients having the hemorrhagic neuroretinitis had the highest values for nonprotein nitrogen of the group and the mortality was 60 per cent.

Of the thirty-six patients, fourteen were known to be living for from three months to two years after the chemical examinations of the blood were made. Eleven of these fourteen patients were improved on leaving the hospital, two were unimproved and one patient was worse. Fourteen patients died and the condition of eight could not be learned. Of the fourteen patients who died, five died of uremia or of uremia and a contributory cause. All five patients with cardiac decompensation died, and postmortem examination of two of these demonstrated a terminal bronchopneumonia. Both had a moderate chronic diffuse nephritis with arteriosclerotic atrophy, and both had a marked sclerosis of the aorta and larger arteries, one patient being syphilitic, the other senile. Four patients died of cerebral hemorrhage. For two, this diagnosis was confirmed by postmorten examination, and both had a moderate chronic diffuse nephritis, one with secondarily contracted kidneys, the other arteriosclerotic atrophy.

There are thirty-nine patients in Group III varying from 27 to 72 years and averaging 52 years. The clinical diagnosis for twelve was cardiac decompensation, for six cardiorenal disease, three essential arterial hypertension and eighteen chronic nephritis with hypertension.

The urine of twenty-seven patients contained both albumin and casts; that of ten, albumin alone; that of one, a few hyalin casts; and neither albumin nor casts in one.

The maximum systolic blood pressure varied from 150 to 268 mm. mercury, the diastolic from 74 to 164 mm. The phenolsulphonephthalein test varied from 20 to 76 per cent. and averaged 42 per cent. for the two hour period. The Wassermann reaction of the blood for syphilis was negative on twenty-six patients.

Dyspnea was the most common symptom and was present with eighteen patients. Twelve patients complained of headache, eight of cough, seven each of pain or distress in the precordium, and nausea and vomiting, six each of frequency of urination and the results of a paralytic stroke some time before, five each of orthopnea, visual disturbances, palpitation, nocturia, dizziness and weakness, four of constipation and pain or distress in the epigastrium, three a generalized edema, and scanty urination, two each had dysuria, migraine, nervousness, sleeplessness, loss of weight and syncope. With seven patients the hypertension had been present for from five to twenty years (average 8.2 years). Hypertrophy of the heart was the most common abnormality found on physical examination in twenty-six patients. Nineteen patients had edema of the feet and legs, which was marked in eight; in twelve patients the liver was enlarged; in ten each there was the systolic murmur of mitral regurgitation and marked sclerosis of the peripheral arteries; in nine there was pulmonary hypostasis; in seven an ascites; in five the aortic second sound was distinctly accentuated; in four there was a marked scrotal edema; in three there was a hemiplegia, and sluggish and unequal pupils; in two each there was a gallop rhythm, a palpable kidney, bilateral hydrothorax and the murmur of aortic regurgitation.

After a period of from two days to two and one half years, twenty-four patients were known to be living, eleven were dead and regarding four no information is available. Seven of the living were unimproved, fourteen were improved and three were worse. Five of the eleven deceased died of "heart failure" and for two of these postmortem examination revealed marked hypertrophy and dilatation of the heart, with marked senile sclerosis and arteriosclerotic kidneys in one, cardiac hypertrophy, dilatation and mitral stenosis in the other; four died of cerebral hemorrhage, and for two of these this was confirmed by postmortem examination; and one of uremia but without necropsy.

No relationship was found between the height of the blood pressure and the degree of nitrogen retention in any of the patients in Group III.

The patients with clinical evidence of myocardial insufficiency including dyspnea, cough, palpitation, engorgement of the liver, and edema of the lower extremities had an increased concentration of uric acid in the blood, average 6.73 mg. as opposed to 3.86 mg. per 100 c.c. for the patients without marked evidence of decompensation. Improvement

of the decompensation was accompanied by a marked diminution in the amount of uric acid in the blood whereas the other nonprotein nitrogen substances of the blood were only moderately decreased in amount.

As a rule, the higher values for blood urea, total nonprotein nitrogen, and creatinin were obtained in those patients where the clinical evidence was in favor of chronic nephritis or where a chronic nephritis was found at postmortem examination.

DISCUSSION

These results are in accord with the observations of other investigators who have studied the functional pathology of the kidneys in chronic nephritis. It has been known for many years that there is an increased amount of nitrogenous urinary waste in the blood of patients with chronic interstitial nephritis. The amount of urea thus retained in the blood was estimated fairly accurately by Herter [3] and was found by him to be increased in chronic nephritis. Concomitant with the rise in the urea nitrogen of the blood is the increased concentration of the total incoagulable nitrogen as has been found by numerous investigators among whom may be mentioned Strauss,[4] Folin,[5] Farr and Austin,[6] Hopkins and Jonas,[7] and Myers.[8]

It is now generally admitted that chronic parenchymatous or degenerative nephritis is not associated with such marked retention of "noncolloidal" nitrogen in the blood as are the various types of chronic nephritis associated with arterial hypertension. In most patients uremia which occurs as a sequel to chronic interstitial nephritis is accompanied by a high concentration of the nonproteln nitrogen compounds in the blood. Very exceptionally does uremia occur without these coincident phenomena and one such patient (blood pressure, 140-150 mm.) has been reported by Foster [9] who found only twenty-eight mg. of non-

3. Herter, C. A.: On Urea in Some of Its Physiological and Pathological Relations. Johns Hopkins Hosp. Rep. **9**:69, 1900.

4. Strauss, H.: Die Chronischen Nieren Entzündungen in ihre Einwirkung auf Blutfluessigkeit and deren Behandlung. Berlin, 68: 1902.

5. Folin, O., Denis W. and Seymour M.: The Nonprotein Nitrogen Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism Arch. Int. Med. **13**:224 (Feb.) 1914; Folin, O. and Denis, W.: On Uric Acid, Urea, and Total Nonprotein Nitrogen in Human Blood. J. Biol. Chem. **14**:29, 1913.

6. Farr, C. B. and Austin, J. H.: The Total Nonprotein Nitrogen of the Blood in Nephritis and Allied Conditions. J. Exper. M. **18**:228, 1913.

7. Hopkins, A. H. and Jonas, L.: Studies in Renal Function with Special Reference to Nonprotein Nitrogen and Sugar Concentration in the Blood. Phthalein Elimination and Blood Pressure. Arch. Int. Med. **15**:964 (June) 1915.

8. Myers, V. C. and Fine, M. S.: The Nonprotein Nitrogenous Compounds of the Blood in Nephritis with Special Reference to Creatinin and Uric Acid. J. Biol. Chem. **20**:391, 1915.

9. Foster, N. B.: Functional Tests of the Kidney in Uremia. Arch. Int. Med. **13**:452 (May) 1913.

protein nitrogen per 100 c.c. of blood. On postmortem examination there was found a marked chronic nephritis (small granular kidneys), edema of the brain and colitis. It is questionable whether such a disease and its termination should be classified with the true uremias or with a group of nephritides designated by Strauss [10] and by Volhard and Fahr [11] as pseudo-uremia.

In Table 2 are contained the estimation of similar waste products noted by others in patients with chronic interstitial nephritis in whom the diagnosis was confirmed by postmortem examination.

TABLE 2.—ESTIMATION OF SIMILAR WASTE PRODUCTS IN CHRONIC INTERSTITIAL NEPHRITIS

Author	Number of Patients	Nonprotein Nitrogen, Mg.	
Frothingham[12]	16	45.7–257.7	
Thayer and Snowden[13]	20	50 –210	
Stengel, Austin and Jonas[14]	5	*102 –195	(uremia)
Strauss[15]	19	68 –266	(uremia)

* Urea nitrogen.

All these patients had a marked increase in the nonprotein nitrogen of the blood during life and as a rule the amount was more than 100 mg. per 100 c.c.

The amount of nonprotein nitrogen in the blood in uremia is usually markedly increased but is subject to marked variations. Values ranging from 28 to 658 mg. per 100 c.c. have been recorded by Strauss, Ascoli,[16] Farr and Austin, Fitz and Rowntree,[17] Widal,[18] Obermayer and Popper,[19] Hohlweg,[20] Foster,[21] Tileston and Comfort [22] and others.

10. Strauss, H.: Ueber Uramie, Berlin klin. Wchnschr. **52**:368, 1915.

11. Volhard, F. and Fahr, Th.: Die Brightsche Nierenkrankheit. Berlin, 1914.

12. Frothingham, C.: The Relation Between Functional Tests and the Pathological Anatomy of the Kidney in Chronic Nephritis, Am. J. M. Sc. **151**:72 1916.

13. Thayer, W. S. and Snowden, R. R.: A Comparison of the Results of the Phenolsulphonephthalein Tests of Renal Function with the Anatomical Changes Observed in the Kidneys at Necropsy, Am. J. M. Sc. **148**:781, 1914.

14. Stengel, A., Austin, J. H. and Jonas, L.: A Comparison of the Functional and Anatomic Findings in a Series of Cases of Renal Disease. Arch. Int. Med. **21**:313 (March) 1918.

15. Strauss, H.: Berl. klin. Wchnschr. **52**:368, 1915.

16. Ascoli, G.: Pfluger's Arch. f. Path. Anat. **87**:103, 1901.

17. Rowntree, L. G. and Fitz, R.: Studies of Renal Function in Renal, Cardio-Renal and Cardiac Diseases. Arch. Int. Med. **11**:258 (Feb.) 1913.

18. Widal, F.: Sem. méd. **25**:313, 1905. Bull. et mem. Soc. méd. d. hôp. de Par. **32**:627, 1911.

19. Obermayer and Popper: Ztschr. f. klin. Med. **72**:332, 1911

20. Hohlweg, H.: Deutsch. Arch. f. klin. Med. **104**:216, 1911.

21. Foster, N. B.: Uremia: The Nonprotein Nitrogen of the Blood. Arch. Int. Med. **15**:356 (March) 1915.

22. Tileston, W. and Comfort, C. W.: The Total Nonprotein Nitrogen of the Blood in Health and in Disease as Estimated by Folin's Methods. Arch. Int. Med. **14**:620 (Nov.) 1914.

Of the various nonprotein nitrogen constituents of the blood, creatinin is the most uniformly increased in uremia, according to Folin and Denis,[23] and Myers and Lough.[24] Myers and Killian [25] found that in chronic nephritis an amount of creatinin in the blood exceeding 5 mg. is of grave prognostic significance. Folin and Denis,[26] Myers, Fine and Lough,[27] Baumann and others [28] believe that uric acid is the first of the nonprotein nitrogen substances to be retained in nephritis.

SUMMARY

The patients in Groups I and II all had definite clinical, functional, chemical (and six patients, anatomical) evidence of nephritis. In the patients with both nephritis and myocardial inefficiency, the uric acid of the blood was in greater amount than in those with nephritis alone. Improvement of the cardiac decompensation was always associated with a decrease in the amount of uric acid in the blood. The average amount of uric acid in the blood of the patients in Group III with cardiac decompensation was considerably higher than that of the patients of Group II with chronic nephritis of moderate degree—the averages 6.9 and 6.06 mg. per 100 c.c., respectively. It would appear, therefore, that greater uric acid retention is associated with passive hyperemia of the kidneys than with chronic nephritis of moderate degree.

The average amount of the uric acid in the blood of the patients of Group III with chronic nephritis was 4.53 mg., whereas that of the patients with myocardial inefficiency alone averaged 6.38 mg. per 100 c.c.

The amount of albumin in the urine and the number of casts could in no way be correlated with the amount of the various nonprotein nitrogen constituents in the blood. Several patients with little evidence of nephritis in the urine had a moderate degree of nitrogen retention whereas a few with a large amount of albumin and many casts had little evidence of kidney insufficiency.

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23. Folin, O. and Denis, W.: On the Creatinin and Creatine Content of Blood. J. Biol. Chem. **17**:487, 1914.

24. Myers, V. C. and Lough, W. G.: The Creatinin of the Blood in Nephritis. Arch. Int. Med. **16**:536 (Oct.) 1915.

25. Myers, V. C. and Killian, J. A.: The Prognostic Value of the Creatinin of the Blood in Nephritis. Am. J. M. Sc. **157**:674, 1919.

26. Folin, O. and Denis W.: The Diagnostic Value of Uric Acid Determinations in Blood. Arch. Int. Med. **16**:33, (July) 1915.

27. Myers, V. C., Fine, M. S. and Lough, W. G.: The Significance of Uric Acid, Urea, and Creatinin of the Blood in Nephritis. Arch. Int. Med. **17**:570 (Nov.) 1916.

28. Baumann, L., Hansmann, G. H., Davis, A. C., and Stevens, F. A.: The Uric Acid of the Blood as Compared with the Renal Dietary Test, Arch. Int. Med. **24**:70 (July) 1919.

CONCLUSIONS

1. Chronic nephritis with hypertension and uremia is characterized by a marked increase in the amount of the nonprotein nitrogen substances in the blood and a low phthalein excretion.

2. Chronic nephritis of moderate degree with hypertension is associated with a moderate increase in the amount of waste nitrogen in the blood and a lessened kidney function.

3. Cardiac inefficiency without nephritis is associated with a moderate retention of the nonprotein nitrogen substances in the blood, more particularly the uric acid.

4. In chronic nephritis with clinical and antomic evidence of disease there is nitrogen retention and renal inefficiency.

5. The presence of albumin and casts in the urine is not necessarily diagnostic of nephritis nor is their absence necessarily indicative of the nonexistence of such disease.

6. Improvement of the circulatory disturbances is accompanied by a decrease in the various nitrogenous extractives of the blood, more particularly the uric acid and this may suggest that, at least, a part of the damage done the kidneys is a sequence of the alterations in its nutrition brought about by passive hyperemia.

A CONTRIBUTION TO THE STUDY OF TUMORS FROM THE PRIMITIVE NOTOCHORD

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The notochord or chorda dorsalis of the amphioxus, in which it is the only axial skeleton, and in fishes and amphibians, in which it is still persistent in the axial skeleton, is of entodermal origin, while in the higher vertebrates the notochordal process and the mesoderm are apparently derived from the ectoderm. In developing embryos of the higher vertebrates, it becomes enclosed in the centers of the vertebrae and in the modified vertebrae forming the base of the cranium, in which sites it eventually and usually early in the mammals, degenerates, with the exception of residuals known as pulpy masses or nuclei pulposi located in the intervertebral discs.

The normal embryonic residual notochord tissue is composed of rather large, round or slightly oval, acidophilic epithelial cells which develop vacuoles containing mucein. In later stages, the cell wall disappears, thus freeing the cytoplasm which fuses with that of other adjacent cells, forming a syncytial structure which is not unlike that of fetal connective tissue. The adult notochord tissue is characterized by large cells containing vacuoles, eccentric, angular nuclei, and is bound together by a syncytial type of cytoplasm.

Abnormal growths of notochord tissue have most commonly been found at the spheno-occipital synchondrosis at the upper end of the notochord behind the pituitary body, and in the sacrococcygeal region, the lower end of the cord, although at least one has been described which occurred at the level of the upper cervical vertebrae.[1] Many of the so-called chordomas are small benign masses of this tissue which has during early development been forced out of the bone, being probably analogous to other better known types of tissue displacement.

Virchow[2] termed these growths from the synchondrosis "ecchondrosis physalifora" because of the vacuolated, degenerated cell surrounded by a bluish hyalin-like substance appearing somewhat like cartilage, and Mueller[3] was apparently the first to be of the opinion that these small masses originate from rests of notochordal cells. These small chordomas, when growing in the cranium, have been

1. Klebs: Allegemeine Pathologie, Pt. 2, 693.
2. Virchow: Entwickelung des Schädelgrundes in den krankhaften Geschwülste.
3. Mueller, H.: Ueber das Vorkommen von Resten der Chorda dorsalis beim Menschen nach der Geburt und über ihr Verhältnis zu den Gallert geschwülsten am Klivus, Ztschr. f. rat. Med. **2**:202, 1858.

known to assume dimensions great enough to produce symptoms of intracranial pressure,[4] but usually, as shown by Ribbert's[5] investigations on these tumors of the region of the clivus, the growths are small and soft, hence do not produce clinical manifestations, are connected by the slender pedicle with similar tissue imbedded in the bone, perforate the dura, and often are attached to the basilar artery. He stated that these small nodules, to which he gave the name chordoma, were found in 2 per cent. of all necropsies.

I have recently removed at necropsy one of these soft pale gelatinous, pea-sized tumors from the clivus blumenbachii. This small growth was attached by a pedicle to a similar structure imbedded in the bone and had perforated the dura. Microscopic examination revealed a pale, basic staining cartilaginous appearing matrix in which there were a few large vacuolated cells with marginal nuclei. (Fig. 6—C).

Fischer[6] first described the malignant chordoma occurring at the base of the skull, and malignant, invasive chordomas of the sacrococcygeal region have been described by Mazzia,[7] Albert[8] and others.

Because of the peculiar vacuolization of cells, the arrangement and staining properties of the matrix and invasive mode of extension, the differentiation of chordoma, myxochondroma and colloid carcinoma is often difficult, and doubtless many errors have arisen in this connection, particularly when the growth has occurred in the sacral region. The few differentiating features will be discussed at the end of this paper.

With the exception of Albert's case, I am not aware of any written reports of these cases in this country, and as instances of malignant chordoma are rare, their pathologic characteristics are not well known, and as four are now available for analysis it seems desirable to publish such an account.

Case 1 came to necropsy in our laboratory at Saint Elizabeth's Hospital. Case 2 was seen by Lieutenant Commander John Harper, U. S. Naval Medical School. Cases 3 and 4 were brought to my attention by Dr. Joseph C. Bloodgood of Johns Hopkins University, who kindly gave permission and material from the records for their publication.

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4. Grahl: Eine Ecchondrosis Physalifora Spheno-Occipitalis Ungewöhnlichen Umfanges, Dissertation, Göttingen, 1903.

5. Ribbert: Zentralbl. f. path. Anat., p. 149, 1894, Geschwülstlehre, p. 149, 1904.

6. Fischer: Ueber ein malignes chordom der Schädelrüchgratshöhle, Beitr. z. path. Anat. u. z. allg. Path., Jena **40**: 1907.

7. Mazzia: Chordom der Sakralgegend, Zentralbl. f. allg. Path. u. path. Anat. **21**:769, 1910.

8. Albert, H.: Chordom, with the Report of a Malignant Case from the Sacrococcygeal Region, Surg., Gynec. & Obst. **21**:776, 1915.

REPORT OF CASES

CASE 1 (1921).—Male, white, aged 54, born in Ireland, soldier, stated that his habits were always good. He never drank to excess, worked regularly and had always been in good health until the age of 23 when he had an acute mental upset which led to his arrest and commitment to the Government Hospital for the Insane, where he remained until his death.

Family history not available.

Physical Examinations at the time of admission and during the following ten years showed no abnormalities. Mentally he was of the paranoid constitution, admitting occasional auditory hallucinations, frequently becoming restless and excited, walking up and down the ward talking angrily to himself in profane and vulgar language.

Present Illness.—Six years ago the patient was described as being neat in dress and habits, sleeping well, and apparently in good physical condition with the exception of "lumbago" pains and external hemorrhoids. A Wassermann reaction at this time was weakly positive, and probably without significance. During the next year there was mentioned that the patient was frequently violently angry at some of his associates and was engaged in several ward fights (possibility of coccygeal injury). A year before death, he had a parole, did fairly efficient work in the dining room, but had a few rather insignificant delusions. His physical health was recorded as satisfactory.

Four months before death it is stated that he was suffering from diarrhea and tenderness of the abdomen. A month later, he complained of gastrointestinal pain, nausea, diarrhea and headache. A large nodular mass surrounding the rectum and bladder, the functions of which were intact, was palpated in the pelvis. There was sufficient abdominal and pelvic pressure to produce severe alterations in the circulation of the thighs and scrotum, which were edematous and cyanotic. Palpation of the body surface showed a boardlike rigidity of the inner portion of the left thigh, and of the abdomen as high as the umbilicus. There was considerable induration about the testicles.

Diagnosis.—A diagnosis of inoperable pelvic malignancy was made.

Clinical Course.—The patient gradually became weaker and more emaciated until death supervened, a little over three months after acute symptoms were noticed.

POSTMORTEM FINDINGS

External Examination (twenty hours after death): The subject was a middle aged man with a slender skeleton and a large type of skull; the body was considerably emaciated, but showed residuals of former powerful muscles. There was a diffuse bluish-yellow cast to the skin. The entire abdomen below the umbilicus was extremely firm and rigid, as was also the area over the adductor group of muscles of the left thigh, as outlined in Figure 1. The boardlike resistance of this area gave one the impression of an ossifying myositis.

The penis was edematous and the testicles were drawn tightly against and attached to the os pubis to the extent of complete immobility. The perineum was also resistant to pressure.

The skin covering these areas was unbroken and evinced no pathologic changes.

Internal Examination: On section of the abdomen, the parietal peritoneum from the level of the umbilicus downward into the bladder region was thick, white, glistening, slightly roughened, extremely fibrous, and had the consistence of cartilaginous structure. Near the pubic bone, the peritoneum averaged from 8 to 10 mm. in thickness, gradually thinning out toward the umbilicus. The landmarks of the pelvic and dorsal peritoneum were completely obliterated by solid continuous sheets of tumor invasion.

Tumor.—The principal mass was now located and found to fill the entire pelvis proper, enclosing the rectum, bladder and other pelvic viscera in a firm encasement. Its broad attachment to the entire sacral curvature from near

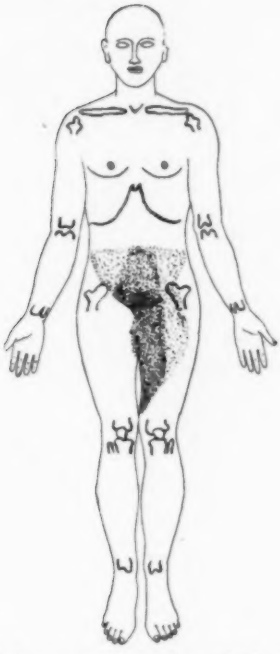

Fig. 1.—The shaded area outlines the extent of surface rigidity.

Fig. 2.—Section of sacrum and coccyx showing the broad attachment of the principal tumor mass to the curvature.

the promontorium to and surrounding the tip of the coccyx is illustrated in Figure 2. Gross sections of the main mass revealed a whitish, firm, inelastic tissue in which small orange-colored fat accumulations were entrapped.

A large fossa was produced in the tumor by the laborious removal of the bladder and rectum. The bladder was sacculated in a long conelike extension at the apex, compensatory to the extreme rigidity and immobility of the remainder of its walls. The ureter was intact and the mucosa of the entire structure exhibited pressure changes and punctate hemorrhages, but no actual erosions.

Prostate.—The prostate gland was under considerable pressure from the surrounding growth which had completely filled the capsule, but had not entered the glandular substance (Fig. 3, B).

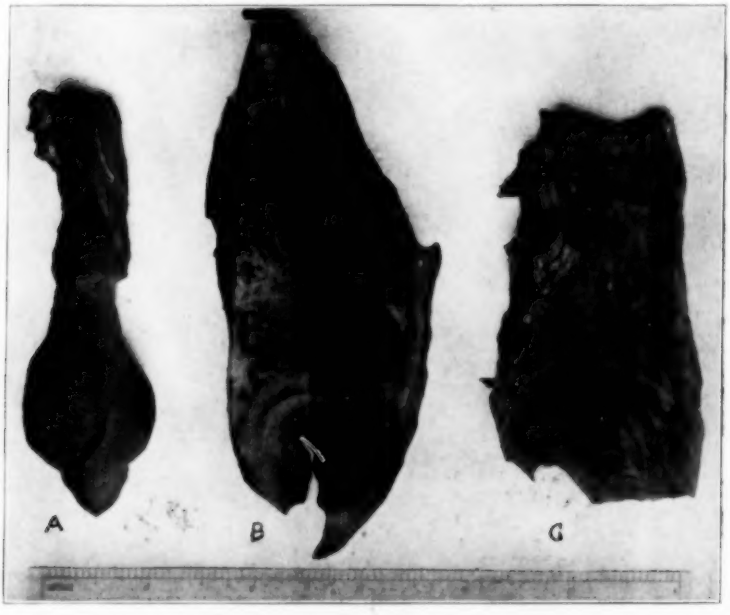

Fig. 3.—A, testicle and cord surrounded by solid tumor growth; B, section of infiltrated bladder and rectal walls with prostate between; C, section of the skin and thickened subcutaneous tissues of the thigh.

Rectum and Sigmoid.—The walls of the rectum and sigmoid were completely infiltrated with foreign growth as far as the mucosa, which showed hypertrophic and advanced hemorrhagic changes; the lumen of the gut was open throughout but distorted. The entire gut, including the sigmoid and lower portion of the descending colon was almost inflexible and reminded one of stiff garden hose. The mesenteries of the colon and small intestines presented a mild but distinct increase in texture, and in patches were tightly attached to the abdominal and pelvic fascias, allowing very little mobility to the intestinal tubes. The growth extended through the mesenteries in a thin sheet with no nodules and without infiltrating the lymph glands, which were normal in size and color. The infiltration of the tumor extended upward as high as the trans-

verse colon but had not affected the walls or attachments of the stomach. The walls of the small intestines were not grossly infiltrated, and the mucous membranes were normal in appearance.

Liver.—The undersurface of the diaphragm, the capsule and ligaments of the liver were not affected. The liver exhibited a diffuse edematous, toxic, congested appearance, with a moderate central lobular degeneration. The gall-bladder was small but contained normal appearing bile.

Spleen.—The spleen was imbedded in a thick, firm, gray capsule of foreign growth, which was not nodular but slightly roughened and enclosed the organ like a case. In general, it stripped easily from the surface, but firmly adhered to the capsule in patches. The substance of the spleen presented productive interstitial changes, but no gross invasion of the tumor.

Pancreas.—The pancreas was surrounded by sheets of tumor growth, which had followed the connective tissue and vessels into the gland, ramifying profusely between the lobules which were affected only by pressure changes.

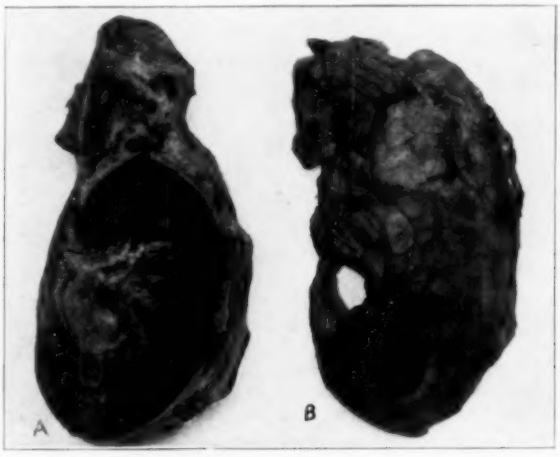

Fig. 4.—A, section of the kidney showing thickened capsule, infiltration of pelvis, and imbedding of adrenal in chordoma extensions; B, kidney capsule diffusely infiltrated with chordoma.

Kidneys.—Both kidneys were encased by neoplastic growth which had fused with and stripped along with the capsule, leaving the surface of the organs corrugated from the prolonged effects of diffuse productive nephritis. Sections exhibited congestion and acute changes through the cortex. The tumor had extended along the ureters and vessels in the pelvis of the organ with extensions through the peripelvic fat and about the papillae (Fig. 4). The ureters were surrounded by the tumor, and the walls were infiltrated, but the lumina were patent.

Suprarenals.—The suprarenal glands were deeply imbedded in the tumor mass (Fig. 4), and showed exhaustion of the medulla, and many minute cortical hypertrophies.

Pelvic Fascia.—Extending from the sacral area through the pelvic fascias, which in places were half an inch in thickness, the tumor spread over the left Poupart's ligament and down the subcutaneous tissues of the inner portion of the left thigh nearly as far as the knee, crowding the adductor group of

muscles beneath it, but apparently not infiltrating them. In places, these subcutaneous tissues were 1½ inches in thickness, grayish in color, and of cartilaginous texture mixed with fat (Fig. 3 C). The subcutaneous tissues of the outer portion of this thigh and the fascia lata were normal in appearance. The tumor had not extended below Poupart's ligament of the right side, but had grown centrally into the tunics of the testicles, completely surrounding but not infiltrating the glandular substance, although radiations could be traced into the mediastinum testis. There was apparently, in addition to the actual tumor, a tremendous fibrous tissue response, so that the structures were bound tightly to the pubic bone. The spermatic cords with their structures and extensions were heavily infiltrated, firm, rounded and had attained the diameter of one-half inch (Fig. 3 A).

Lungs.—Detailed examination of the thoracic viscera revealed neither evidence of tumor extension above the diaphragm nor gross metastases.

The lungs were both free in the pleural cavities, with the exception of a few well organized adhesions at the left apex, and the upper lobes were collapsed. Section revealed normal upper lobes, while the lower lobes of both organs showed a moderate congestion and edema without consolidations. The mucous membranes of the trachea and bronchi appeared somewhat anemic.

Thyroid.—The thyroid revealed a reduction in the amount of colloid and advanced interstitial changes.

Heart.—The heart was in normal position, and the pericardium was not remarkable. The muscles were rather pale in color and the cardiac veins considerably distended. In general, the organ was normal considering the age with valves in good condition and only a slight interstitial myocarditis. Aorta was normal with the exception of a mild fibro-fatty plaque production.

Skull.—The skull was thin throughout but the parietal bones were extremely so. The dura mater was slightly adherent to the calvarium and thickened to the extent that the brain convolutions were not easily visible through it. The cerebrospinal fluid was apparently normal.

Brain.—The brain weighed 1,200 gm. and was remarkably anemic, the larger veins being empty and the smaller capillaries barely visible. The brain substance was universally edematous, and the arteries of the base showed a few discrete arteriosclerotic nodules, but otherwise there were no gross abnormalities.

Pituitary.—The pituitary gland with the sella turcica was not unusual.

MICROSCOPIC EXAMINATION

Sections from Sacral Tumor: The connective tissue response through these sections was remarkable and large bands of this structure were filled with the characteristic cells of malignant notochordal tissue. In many places there were localized groups of large vacuolated cells, bearing eccentric nuclei of various sizes, and lying in a pale, finely granular matrix, while in other fields these cells were thinly scattered through the fibrous tissue.

In some areas there were many variations in the cell structures and type of arrangement. The classification I offer is descriptive of the types frequently encountered (Fig. 5).

1. Cells with thin rim of finely granular protoplasm, a single large central vacuole which has often ruptured the enclosing protoplasm, and a marginal nucleus which varies in size, staining properties, and is often multiple (b).

2. Cells with a heavily stained, irregular nucleus only slightly eccentric and with relatively more protoplasm bearing several large sized vacuoles (a).

3. Cuboidal, polyhedral or columnar cells with central irregular nucleus and protoplasm with a few small vacuoles (c).

4. Large cuboidal or columnar cells with a narrow, marginal, irregular, heavily stained nucleus, and relatively large amount of protoplasm containing a few small vacuoles (d).

5. Slightly irregular cuboidal, polyhedral or rounded cells bearing a relatively large granular nucleus and without vacuoles in the protoplasm (c).

6. Irregular and compound cells with peculiar arrangements of the nucleus and protoplasm—formed probably by fusion of cells after partial discharge of mucein or by cell division under pressure (f).

Sections of Skin and Subcutaneous Tissue.—The skin layers, the hair follicles, sebaceous and suderiferous glands were apparently normal; however, about some of the lower sweat glands, chordoma cells were seen proliferating, often lying up tightly against the basement membrane. The fibroblastic and fatty elements of the subcutaneous tissues were enormously increased and diffusely infiltrated by the foreign cells, bunches of which were accumulated

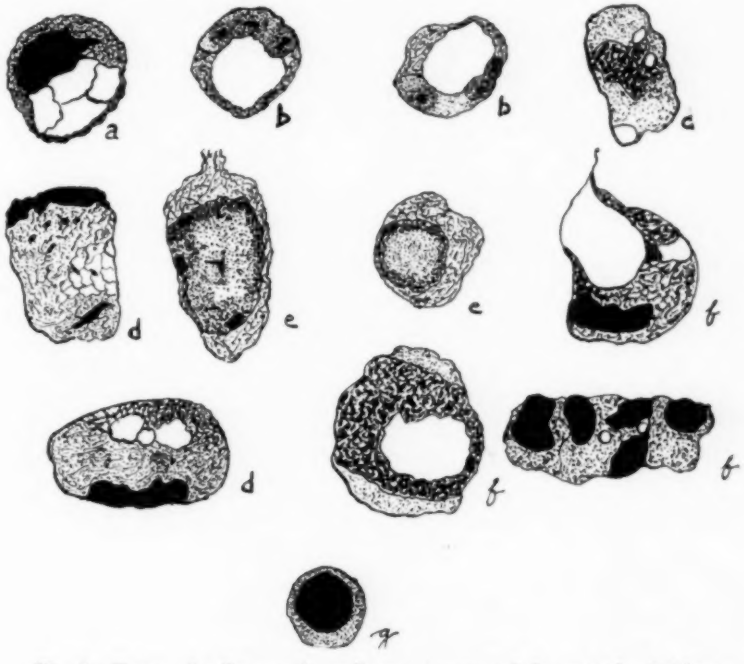

Fig. 5.—Types of cells seen in malignant tumors of the notochord (drawn to same scale). (a) Cells with heavily stained, irregular nucleus only slightly eccentric and with relatively more protoplasm bearing several large sized vacuoles. (b) Cells with thin rim of finely granular protoplasm, a single large central vacuole which has often ruptured the enclosing protoplasm, and a marginal nucleus which varies in size, staining properties and is often multiple. (c) Cuboidal or columnar cells with central irregular nucleus and protoplasm with a few small vacuoles. (d) Large cuboidal, columnar or polyhedral cells with a narrow marginal irregular heavily stained nucleus and relatively large amount of protoplasm containing a few small vacuoles. (e) Slightly irregular, cuboidal polyhedral, or rounded cells bearing a relatively large granular nucleus and without vacuoles in the protoplasm. (f) Irregular and compound cells with peculiar arrangements of the nucleus and protoplasm, formed, probably, by fusion of cells after partial discharge of mucein or by cell division under pressure. (g) Small lymphocyte for comparison.

in the more areolar portions of the tissue. Deep in the tissues, near the muscles, there was a notable lymphocytic reaction with quite dense fibrosis of the structures. In these deeper layers the chordoma cells showing multilobulated nuclei, sometimes central, generally eccentric and occasionally scaphoid, and always situated in a relatively large amount of pale blue protoplasm, were in small groups numbering from three to eight cells per group.

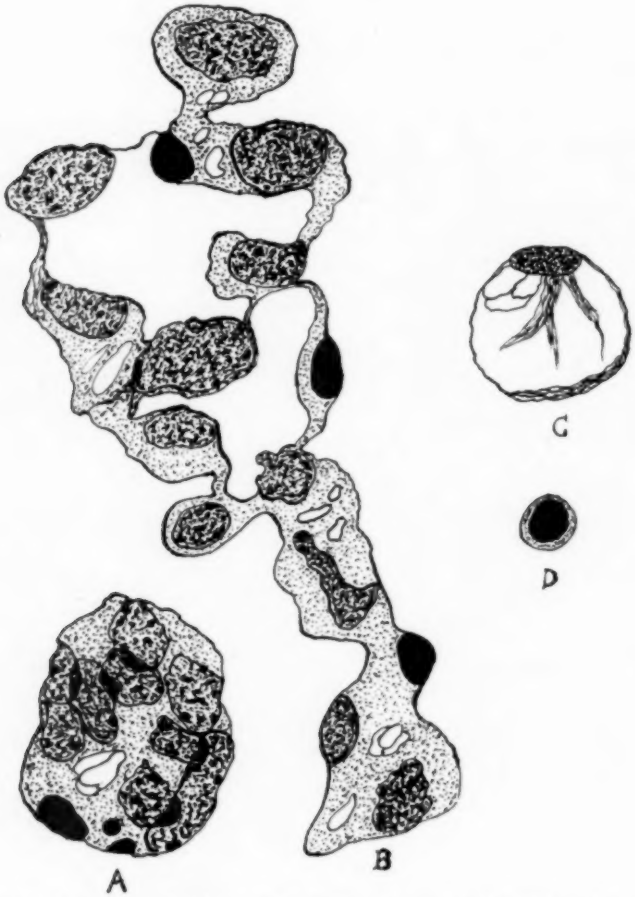

Fig. 6.—A, nests of chordoma cells as seen in mesenteries and tunica vaginalis of the testicles; B, type of cell arrangement seen in all four cases of chordoma—fusion of cell walls, discharge of mucein, and formation of vacuolated syncytial like structure; C, type of benign chordoma cell; D, small lymphocyte for comparison.

The blood vessels of this area were thickened but nowhere were foreign cells seen penetrating the walls, but doubtless many of the smaller arterioles were obliterated by extensions of cells. One large subcutaneous artery was surrounded by chordoma cells, but the walls proper were not affected. The

accompanying nerves with their sheaths were also surrounded but not infiltrated, however, in some sections of the compound fasciculae, a few chordoma cells were seen between the nerve bundles in the epineurium.

The small regional lymph glands showed a dense obliterative central fibrosis and an irregularly thickened capsule from which extensions radiated into the glandular tissue greatly reducing the lymphoid elements. The surrounding tissues were filled with malignant chordoma cells but none had entered the lymph glands.

Fig. 7.—Photomicrograph of section of rectal wall in Case 1, showing large vacuolated cells with eccentric nuclei separating bundles of muscle and connective tissue.

Sections of Mesenteries.—There was a fibrous tissue increase in wide bands throughout, with many large areas of fat cells in which were seen accumulations of rapidly dividing chordoma cells arranged in nests (not unlike carcinomatous formations) often containing as many as twenty-five or thirty cells (Fig. 6 A).

The lymph gland capsules were enormously thickened, fusing with the surrounding structures, and were infiltrated with actively growing tumor cells, but the glands themselves, although they exhibited considerable increase in stroma

were not infiltrated by these cells, all extensions of which appeared to stop at the inner capsular margin.

Walls of Rectum.—The walls of the rectum showed a dense infiltration of all coats with chordoma cells of both the lower embryonic type, and of the older vacuolated eccentric nucleated variety which extended along the fascias between the muscle bundles (Fig. 7) and into the submucosa. The mucosa was not remarkable with the exception of occasional small sized necroses probably produced by pressure changes.

Prostate.—The prostate gland presented a universal adenoplasia of first degree, with irregularity of the acini and hyperplasia of cells, and with considerable concretion deposits in the centers of the follicles. There were no tumor cell extensions in the vicinities of the prostatic glands, with the exception of an occasional small patch of widely separated cells usually situated near one of the acini, but in the fascias surrounding the prostate and between it and the bladder walls and rectal walls there were both nested groups and diffuse infiltrations of chordoma elements of the darkly stained, large nucleated types in a matrix having a high mucein content.

Testicles.—The testicular acini were characterized by a thickened basement membrane, with the attached spermatogenic cells greatly reduced in number and with no spermatozoa. The interstitial tissues were sclerotic throughout. The tunica vaginalis and tunica albuginea were fused and enormously thickened. The tumor infiltration in these regions was patchy in distribution, and in places nests of small dark nucleated chordoma cells, surrounded by clear spaces, gave the general appearance of carcinomatous arrangement; however, the peculiar pale staining mucinous matrix was differential. Neither the acini nor the interstices of the glands proper had been attacked, but the process was limited to the envelopes of the organ, and extended along the spermatic cord, following the fascias, and widely separating its structures, principally from the associated tremendous fibrous tissue production.

Sections of Kidney.—(Description common to both kidneys.) The capsule of the organ was greatly thickened, being a dense, almost solid mass of chordoma cells which filled the entire capsule and were lying close to the glandular margin, but had not dipped down between the cortical structures excepting where the capsule had been followed. The tumor cells of this region were in a connective tissue stroma and representatives of all cell types of Figure 5 were noted.

The outer zones of the kidney cortex were densely sclerotic and in patches only the knotty remains of tubules and glomeruli were seen. Many convoluted tubules were hyperplastic with a slight granular exudate in the centers. Deeper in the cortical structures, the glomeruli were somewhat swollen and hemorrhagic, and the tubules were distorted, the cells which were originally flattened exhibiting advanced albuminous degeneration. In a few areas dense intratubular and extratubular hemorrhages were noted, and the stroma, in general, was increased throughout the organ.

Suprarenals.—The tissues surrounding the glands had fused with those of the kidney, and contained many thickened vessels and wide zones of fibrosis with a large amount of fat and areolar tissue.

Scattered discretely through these tissues, and particularly in the areolar areas were both isolated and small accumulated groups of tumor cells, without infiltration of the suprarenal cortex. The cortex of the gland showed considerable atrophy with a few localized compensatory glandular hypertrophies. The zona glomerulosa remained only in a few marginal knots, and the lower zones appeared to be degenerated and exhausted. The medullary portion was heavily sclerotic, narrowed and presented much lymphatic infiltration.

Liver.—The capsule was thin but fibrous, and showed no evidence of infiltrating tumor cells. There were no tumor cells through the sections taken from the organ, but the substance exhibited diffusely scattered blood pigment and an irregularly distributed fatty degeneration extending through the lobules and about the central lobular veins.

There was a numerical reduction in the liver cells, and the remaining ones were swollen, pale and often vacuolated. A moderate increase in connective tissues was noted in the portal canals.

Pancreas.—Through most of the organ there was a dense sclerosis with complete atrophy of about half the acini, the remaining ones being bunched in small groups and presented heavily stained cells. The islands were distorted and sclerotic showing a reduction in the number of cells. In the fascias about the gland many irregular groups of chordoma cells, held together by a mucinous stroma, were surrounded by fibroblastic productions. These tumor cells had followed the interlobular stroma for short distances into the gland, but in no instance were the tubules involved, excepting perhaps by pressure.

Spleen.—The capsule was thickened, sending ramifications of large size into the substance of the organ, and contained considerable dark brown pigment,

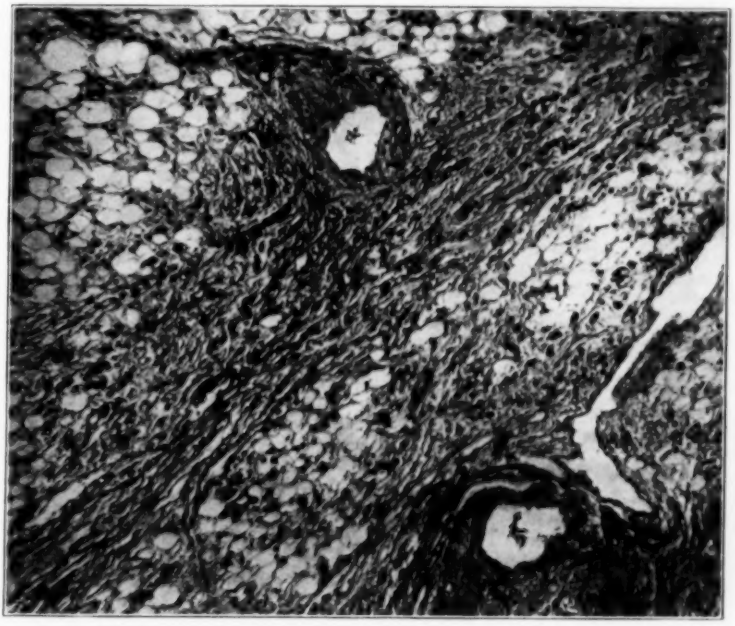

Fig. 8.—Photomicrograph of chordoma cells scattered among the connective tissues and fat cells of the mesenteries (Case 1).

but there were no chordoma cells in the sections studied. There was a general increase in splenic stroma, particularly about the vessels, the malpighian bodies were small and the arterioles were thickened and occasionally hyaline.

Lungs.—No tumor metastases were seen in the lungs, which were not remarkable, with the exception of some congestion of the alveolar arterioles and a peribronchial round cell infiltration.

Thyroid.—The interfollicular structures were filled with epithelial and lymphoid cells and the colloid was diminished to about one-half the usual amount. Wide bands of connective tissue excessively lobulated the organ.

Heart.—The muscle fibers showed some separation and replacement, the muscle cells were pale and atrophied, bearing pale granular nuclei, at the poles

of which was a large amount of brown pigment. An occasional large endothelial cell was noticed between the muscle fibers.

Cerebral Cortex.—There were no unusual changes, with the exception of mildly edematous perivascular lymph spaces and some thickening of the overlying meninges.

Cerebellum.—The meninges covering the leaflets and extending into the fissures showed fibrosis and some endothelial hypertrophies. The architecture of the cerebellar layers was not remarkable, but there was some reduction in the number of purkinjean cells, with a neuroglial felting of the areas.

Spinal Cord.—The cord presented no striking changes, but there was some overlying chronic meningitis and an unusually large number of modified ependymal elements in the central canal region.

Section Including Pelvic Sympathetic Ganglia.—Large patches of chordoma cells were present in sections in which the associated connective tissue response was much less in evidence.

The sympathetic ganglia were surrounded by, but not infiltrated with, tumor cells. Many of the ganglion cells were shrunken, heavily pigmented and surrounded by large pericellular spaces. Some of these cells were acidophilic in reaction, and a few were completely disintegrated.

Pituitary.—The posterior lobe showed dense sclerosis and considerable brown pigmentation, while the anterior lobe was only moderately sclerotic, and the acini were large, well stained and in a good state of preservation.

Case 2 (U. S. Naval Hospital).—A male, white, aged 30, with negative family, past and venereal histories, was admitted to the hospital June 2, 1919, with a history of persistent constipation, with no passages of feces for five days. Vomiting started twenty-four hours after admission, and because of increasing abdominal symptoms a laparotomy was done June 4. All intestines were found to be dilated with fluid, and an annular mass about one inch in length, and of the thickness of a thumb was found obstructing the sigmoid. This mass, with the sigmoid, was fixed to a "stab wound" of the left side and resected four days later (artificial anus). The tumor was diagnosed as carcinoma.

A second laparotomy was done Oct. 20, 1919, which showed the large intestine and peritoneum to be covered with small nodules, which were clinically considered to be either carcinoma or tuberculosis. The pathologic diagnosis from sections of the peritoneal nodules was sarcoma.

Nov. 4, 1919, an operation was done for rectal fistula, which had formed, with resection of the lower rectum, and another laparotomy again showed many nodules over the omentum, but the tumors seemed smaller and less numerous than at the previous operation.

Death occurred Feb. 25, 1920, with clinical evidence of intestinal obstruction. There was a very slight emaciation of the body and tumor masses were palpable through the abdominal wall.

NECROPSY

A necropsy was performed, and the parietal peritoneum, the omentum, the mesenteries and the intestinal walls were studded with small nodules like those seen at the operations. The intestinal obstruction had been caused by a large mass of tumor about 6 inches through, involving the omentum, descending colon and sigmoid. Several associated smaller masses were noted, with enlargement of the retroperitoneal and mesenteric lymph glands.

The liver was congested and exhibited small nodules of tumor tissue in the capsule but none in the substance, and there were no metastases into the thorax.

Microscopic Findings.—Sections taken from the wall of the resected rectum showed the muscle bundles to be separated by round and cuboidal, rapidly multiplying cells; having clear vacuolated protoplasms, and deeply stained, irregular eccentric and often multiple nuclei, surrounded by an abundance of chronic inflammatory tissue. Sections including the mucosa presented no

remarkable changes in this structure nor in the immediate submucous tissues, but the tumor infiltration was rather limited to the muscular layers No malignant changes were noted in the mucosa or skin of the mucocutaneous junction at the anal opening.

Sections of the intestinal walls taken at the necropsy gave the impression of a more rapid growth of the tumor than those taken previously at operation. The streaks of malignant cells had split the muscle fibers into narrow fine strands of tissue, which were atrophied, forming a stroma in places around the individual cells or small groups of cells, although, in general, there was very little tendency to the type of grouping seen in Figure 6 (A and B). A large majority of the cells were closely packed and of the large vacuolated variety with eccentric nuclei (Type 1 of classification), with less surrounding connective tissue reaction than in the earlier sections, and apparently rapidly extending (Fig. 9). None of the larger vessels were penetrated by the growth.

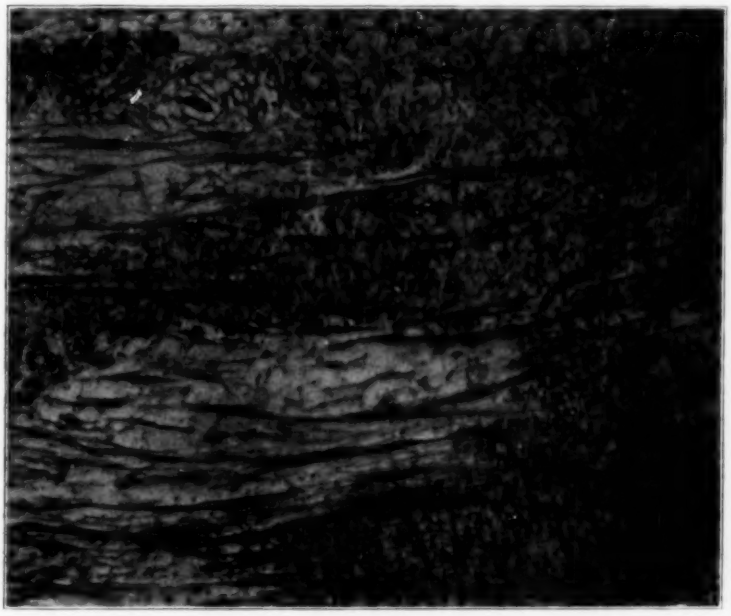

Fig. 9.—Photomicrograph of section of intestinal wall from Case 2 demonstrating rapid infiltration of chordoma cells in the muscular layers.

All the tissues examined from this case were of the above type of reaction, and no evidence of carcinomatous changes or tuberculous lesions was discovered.

Case 3 (Case of Dr. Riggs, South Dakota).—White, male, aged 58, merchant with a negative family history, and a personal history which was negative until two years before operation, at which time he complained of frequent urination with burning. Cystoscopic examinations were negative and the condition was relieved by passing urethral sounds.

The patient entered a hospital in May, 1920, complaining of pains in the rectal region, the right leg, and also in the arms, and he felt chilly. He remembered that during the past two years he had had some discomfort about

the rectal region, occurring usually in the night, and relieved by changing the position. His condition was diagnosed as ischiorectal abscess.

Physical Examination.—This revealed a normal chest, abdomen and prostate. The tonsils were small and "positive." Blood pressure, 88-92/60.

Dorsally, at the lower portion of the coccyx was a mass about the size of a prostate, composed of two distinct nodules, slightly movable, apparently not attached to the rectum, and of the consistence of fibrolipoma.

Treatment.—The tonsils were removed. The blood pressure became better (110), and the tumor was excised.

Tumor.—The growth measured 6 by 5 cm. in two diameters, was enclosed in a definite but thin capsule (Fig. 10), and contained one piece of bone suggesting the tip of the coccyx. The tissue seemed very cellular, with a fine stroma, and was dark brown in color, with gray and white areas. The substance was friable, and some small granular, elevated masses were easily picked from the tissue. The structure did not suggest chordoma or cancer in a dermoid, but was not unlike a giant cell tumor belonging to the type of malignant sarcoma.

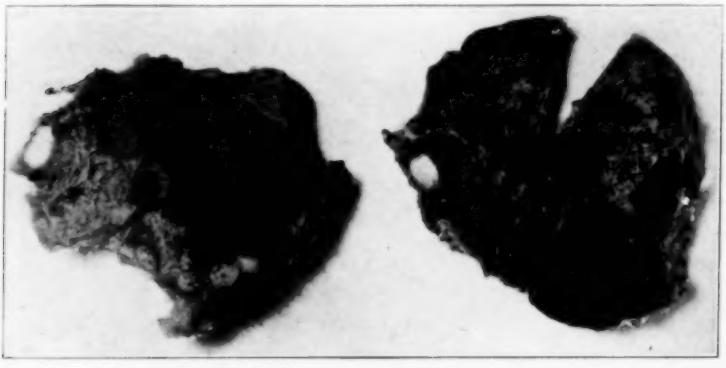

Fig. 10.—Gross sections of the chordoma removed from the rectal region in Case 3.

Microscopic Examination.—This revealed a very cellular structure, with a tendency to alveolus formations, with separations by wide dense strands of eosin staining, hemorrhagic, fibroblastic tissue, which in places included small groups of cells. The cells rested on this and grew out in capillary masses, with fusion of cytoplasm and exudation of mucein, but with no definite intercellular substances. The cells in the center were undergoing disintegration leaving mucein and an eosin staining débris.

The predominating types of cells were cuboidal and round with a lightly staining protoplasm, while the nuclei were large, granular, centrally situated (Fig. 5 E), and showing many forms of karyokinetic figures. There were a few areas showing vacuolated cells bearing the half moon eccentric nuclei typical of chordoma; there were also a few multinucleated cells of giant cell dimensions.

Case 4 (Sent in by Dr. Bassett, Savannah, Ga.).—In September, 1914, a white female, aged 22, applied for relief on account of constant pain in the rectal region. Othewise she was in good condition, showing no loss of weight. Two years before a surgeon had excised a portion of a rectal tumor, which he diagnosed as cancer.

Rectal Examination.—A small hard nodular, irregular mass about 2 inches long was situated at the left side of the rectum and attached to the pelvic fascia, but was not attached to the wall or mucous membrane.

The rectum was incised and a specimen removed. The condition at this time was thought to be quite independent of any previous operation. The possibilities of carcinoma, endothelioma and tuberculosis were considered. The specimen removed for examination was a small piece of firm, white tissue resembling a gland, and at the time was thought to be probably of epithelial origin.

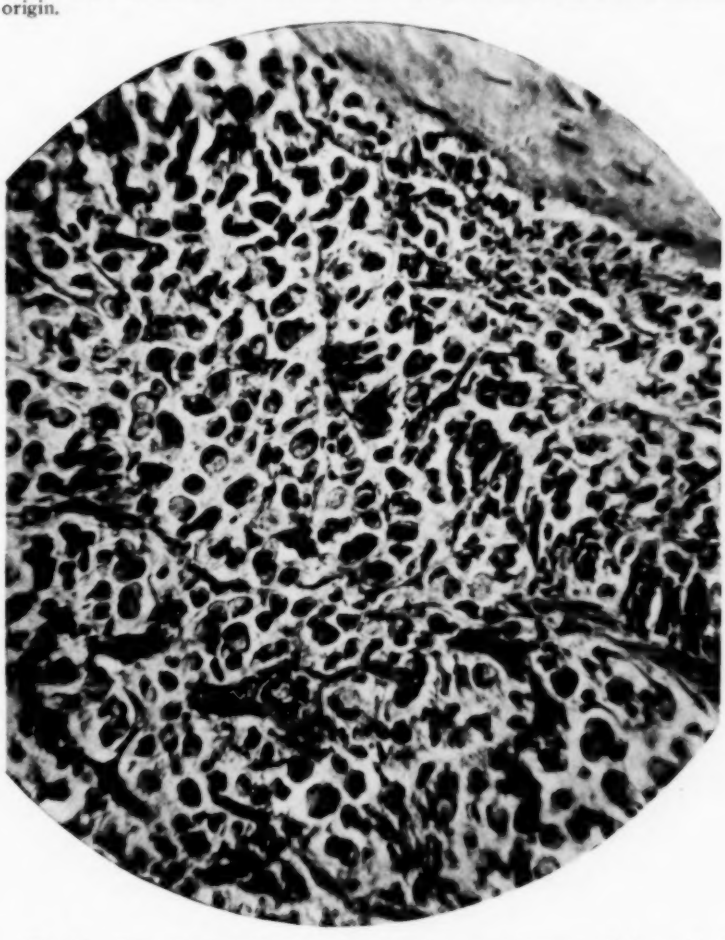

Fig. 11.—Photomicrograph of section taken from tumor metastasis in cervical region in Case 4, illustrating the varieties of cells characteristic of malignant chordoma.

About a year later (October, 1915) the tumor recurred at the rectum with complete obstruction, necessitating opening of the sigmoid above (artificial anus). The patient was now considerably emaciated, and a lump the size of an apple (probably metastasis) had grown in the neck.

Microscopic Examination.—The specimen removed from the rectal region showed a few irregular masses of dense bone, in the meshes of which malignant vacuolated cells of polyhedral and round outlines, with eccentric nuclei, were distributed. These cells resembled those seen in the other three cases, but, on the whole, were somewhat smaller, and showed a pronounced tendency to small groupings in dense connective tissue. The stroma of this tumor was abundant, and many areas of areolar tissue were filled with ringlike cells.

The blood vessels were all thickened, but not, as a rule, penetrated, although in one instance chordoma cells were noted growing in the walls and in the central portion of a thrombosed artery.

At death there were several other masses in the cervical lymph glands, the size of large walnuts. A necropsy could not be obtained, but a tumor was taken from the neck for diagnosis.

The microscopic characteristics were like those of the original tumor from the rectal area, with the exception of being more cellular and with less connective tissue production, and sections exhibited the various types of cells described above for the other tumors and are well illustrated in Figure 11, a photomicrograph from the tissues of this case.

CONCLUSIONS

1. In the majority of cases of chordoma reported the tumor occurred in the spheno-occipital region, so that it is rather singular, but fortunate, to have four instances of this type of malignancy growing from the sacrococcygeal site, giving an opportunity for comparative studies.

2. There is no history suggesting the etiology in Cases 2, 3 and 4, but in Case 1 there is a strong probability of injury to the coccygeal area, and as this region is the site of frequent trauma, the possibility of injury as a causative factor must be considered. (A definite history of traumatism was obtained in the case reported by Albert.)

3. Compartive Summary: In Case 1 the symptoms (diarrhea, nausea, abdominal tenderness and headache) became severe enough to attract attention only four months before death, during which time emaciation and cachexia developed rapidly. This patient was an insane man, in whom subjective symptoms may have been and probably were present long before his condition was complained of or came to the attention of the physician.

A complete necropsy was performed which revealed the principal tumor broadly attached to the sacrum and coccyx, from which site extensive invasions, associated with tremendous connective tissue productions, had radiated through the fascias, capsules and walls of the abdominal organs without infiltrating glandular structures or affecting mucous membranes, except by pressure. The inhibiting effects of this diffuse growth on the functions of the abdominal viscera must have been considerable. There were no true metastases nor nodular formations in the path of the tumor.

In Case 2 death occurred about eight months after the onset of acute symptoms (persistent constipation, vomiting, increasing abdominal symptoms). Early laparotomy showed obstruction of the sigmoid,

and a later laparotomy revealed many small nodules in the peritoneum and in the large intestine. A rectal fistula formed, which was corrected, and a third laparotomy showed many nodules over the omentum.

In this case the emaciation of the body was slight. A necropsy was performed. No mention was made of a tumor attached to the sacrum, but a large mass was described involving the omentum, sigmoid and descending colon, as well as a general distribution of many small nodules in the peritoneum, mesentery and intestinal walls. This feature of growth was quite different from that observed in Case 1.

The earlier sections from Case 2, taken from the resected rectal wall, exhibit a liberal connective tissue response with relatively few chordoma cells, while those taken from the intestinal walls at necropsy were rich in tumor cells and with less connective tissue—showing, in general, a more rapid growth, as in Case 1 no metastases were seen in the thorax.

One patient (Case 3) gave a history of rectal discomfort for two years before the acute symptoms (chilliness, rectal pain, pains in legs and arms) began. A slightly movable, irregular, mass was palpated at the lower portion of the coccyx. This mass measuring 6x5 cm. was excised and found to correspond microscopically with the characteristics described for chordoma. The operation was performed about a year ago. The present condition of the patient is not known to me.

The last patient (Case 4) sought relief from acute symptoms (constant pain in rectal region) a little more than a year before death. At the time of the acute onset she was apparently in good general physical condition, but rectal examination revealed a small, firm, nodular tumor outside the rectal wall in the pelvic fascia. A year later, the tumor in this area produced complete obstruction of the rectum necessitating sigmoid resection (artificial anus). The patient then showed emaciation, and metastases were forming in the cervical region. Death followed, but no necropsy was performed, although a nodule was taken from the neck for diagnosis.

The cells and general structure of the metastasis were those of the original rectal tumor.

It is regretted that a necropsy could not be obtained in this case, as apparently there was a true metastasis to the neck, and it would have been instructive to observe the mode of extension, if any, through the abdominal viscera.

4. So few of these tumors have been recognized and reported that one hesitates to offer an opinion as to their frequency, but that they are of far more clinical importance than has heretofore been considered is quite evident, and judging from the variety of diagnosis made in the four cases cited by as many competent pathologists and surgeons, these tumors are much more frequent than was formerly

supposed, and they have undoubtedly occasionally been classified among the other forms of malignancy.

A differentiation of chordoma from myxochondroma and from colloid carcinoma of the rectal region is not readily accomplished, as the types of cells are often similar, and many other features, such as mucein content, cell formations and stroma arrangements are seen in common. The absence of actual cartilaginous formations speaks against myxochondroma, and broad attachments to the sacrum, with extensive infiltrations through the supporting tissues, and at the same time exhibiting a tendency of limitation to the capsules of organs and glands, avoiding actual glandular structures, and the infrequency of metastasis, are features pointing toward chordoma rather than colloid cancer.

5. Malignant chordoma may be considered as causing 100 per cent. mortality. Because of the extensive infiltration of the regional fascias, and the difficulty of early diagnosis, operative treatment probably rarely effects a cure, but, of course, excisions of the principal tumor mass, and intestinal resections have been beneficial in the removal of pressure and pain phenomena.[9]

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9. The following references also bear on this subject:
Ewing: Neoplastic Disease, 1919, p. 188.
Mallory: Principles of Pathologic Histology, 1914, p. 400.
MacCallum: Textbook of Pathology, 1918, p. 1022.
Adami: Principles of Pathology **1**:761, 1910.

FURTHER OBSERVATIONS ON EXPERIMENTAL LESIONS OF THE BRANCHES OF THE AURICULOVENTRICULAR BUNDLE OF THE DOG*

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CHICAGO

In some work [1] recently reported, lesions of the left branch of the auriculoventricular bundle were produced by incising the endocardium of the left ventricle. It was noted that dogs often gave a normal electrocardiogram even after extensive incisions had been made in the endocardium. Later, however, as the heart became dilated because of experimental ligation of coronary arteries, the electrocardiograms were abnormal.

In this paper are recorded further observations that have been made following the division of the right and left branches and the subdivisions of the left branch of the auriculoventricular bundle. The extent to which the subdivisions of the left branch can be divided and the electrocardiogram still remain normal are in a measure determined. It is further shown that some of the atypical electrocardiograms may be brought back to normal.

In a series of thirty dogs [2] the right branch was divided in eight instances, the left in six and the subdivisions of the left branch in sixteen. The same method was used that was employed in the former work. Care was taken to divide the branches of the auriculoventricular bundle with a minimum damage to the cardiac musculature. We were successful in most instances in producing lesions of the conduction system with no other apparent disturbance of the function of the heart, except that of the transmission of the impulse.

Lesions of the Right Branch of the Auriculoventricular Bundle.—In eight dogs the main stem of the right branch was divided in the neighborhood of the region shown in Figure 1. The incision in six instances extended just through the endocardium. Following the incision there was an immediate change in the contraction of the heart

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* From the Medical Department of Rush Medical College and Presbyterian Hospital.

* This investigation was aided by funds given by Madam C. H. McCormick and R. T. Crane, Jr.

* Read before the Chicago Society of Internal Medicine, Dec. 20, 1920.

1. Smith, F. M.: Experimental Observations on the Atypical Q R S Waves of the Electrocardiogram of the Dog, Arch. Int. Med. **26**:205 (Aug.) 1920.

2. These dogs were fully anesthetized.

that was recognizable by the naked eye. The ventricular chambers were apparently not contracting synchronously. This change in the contraction was so characteristic that we knew when the right branch was divided before taking the electrocardiogram. Other than the change in the contraction wave, the function of the heart was seemingly not disturbed in those instances in which the incision did not extend into the deeper layers of the musculature. The heart remained normal in size and appeared able to withstand an increased load as well as the normal heart.

Those dogs in which there was a complete division of the right branch of the auriculoventricular bundle gave a characteristic electro-

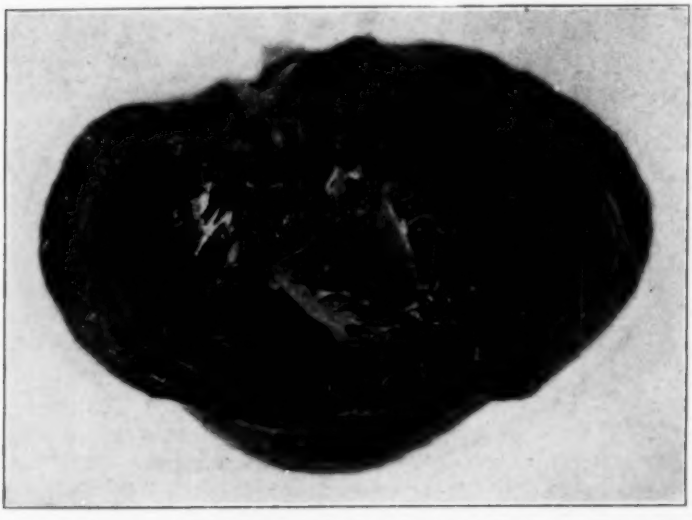

Fig. 1.—Arrow points to the incision on the right side of the interventricular septum. This incision divided the right branch of the auriculoventricular bundle.

cardiogram (Fig. 2). There was a marked S-wave in Leads II and III followed by a positive T deflection. The S-wave was usually notched or slurred at the apex and the duration of the Q R S group was prolonged. The most prominent ventricular wave in Lead I was negative in five instances and positive in three.

The same type of electrocardiogram was obtained when a transient block of the right branch was produced by pressure. In one dog, slight pressure was made for a few seconds over the right branch. This caused a block of the impulse over this branch. The right coronary artery was then ligated and the right ventricle soon became

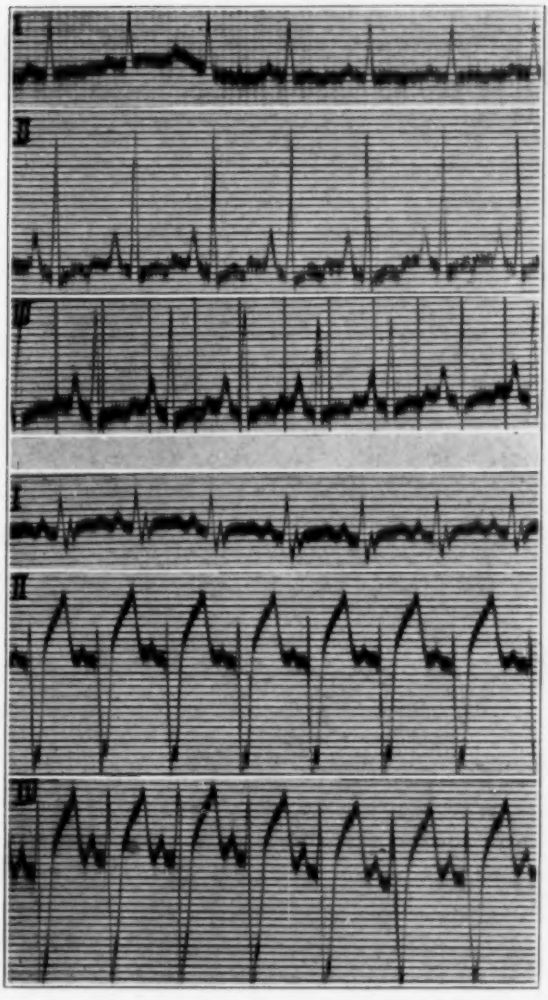

Fig. 2.—Top: Normal electrocardiogram of the heart shown in Figure 1. Bottom: Electrocardiogram taken after the right branch was divided.

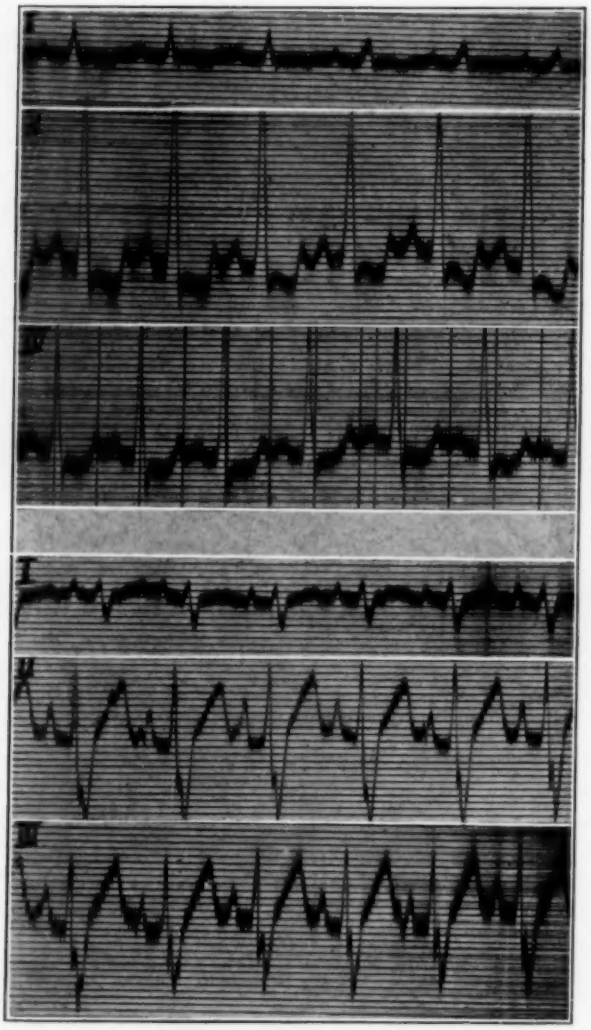

Fig. 3.—Top: Normal electrocardiogram. Bottom: Record taken after pressure was made on the right branch.

markedly dilated. The ligature was allowed to remain on the artery for one and one-half hours. During this time, a right bundle branch block persisted. As soon as the ligature was removed from the right coronary artery the right ventricle returned to the normal size and impulses began to pass over the right branch. Possibly, the temporary ligation of the right coronary delayed the return of the function of the right branch. In an experiment previously reported [3] an electrocardiogram typical of that of right branch block appeared on the second day following the ligation of the right coronary artery.

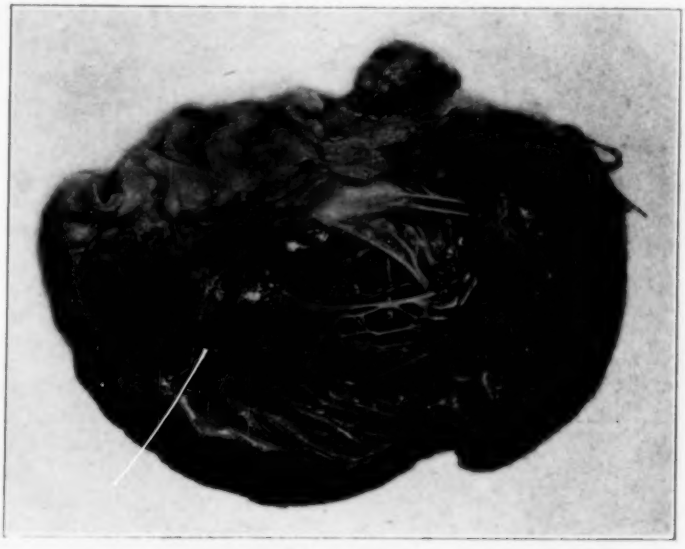

Fig. 4.—Shows several ragged incisions in the endocardium of the left ventricle below the point where the left branch breaks up into subdivisions. All the main subdivisions of the left branch were divided.

Lesions of the Left Branch of the Auriculoventricular Bundle.—Because of the location of the left branch of the auriculoventricular bundle on the under surface of the septum, and its early breaking up into subdivisions, it was a difficult matter to divide the main stem of this branch with one incision. A small incision placed in the right position beneath the aortic valves would accomplish the desired results. It was, however, found to be a more certain procedure to depend on two or more small incisions just below the point where the main branch breaks up into subdivisions (Fig. 4).

3. Smith, F. M.: Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918.

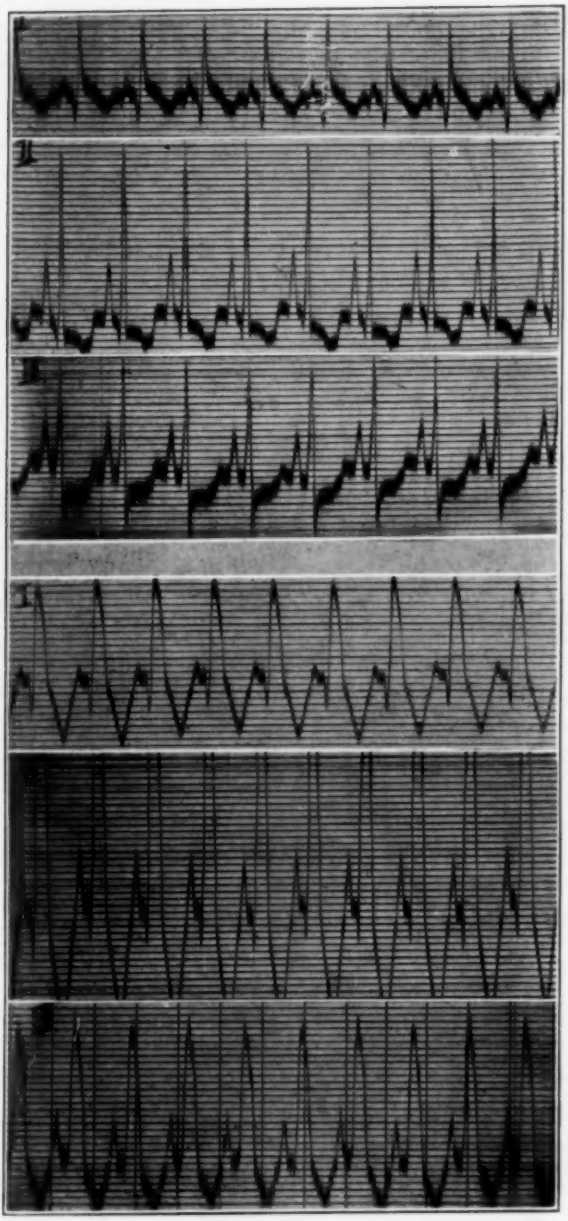

Fig. 5.—At the top is the initial electrocardiogram of the heart in Figure 4. The record at the bottom was taken after the incision was made in the endocardium.

In six dogs, the left branch was divided at the latter point. This was accomplished in four instances with but a small amount of damage to the ventricular musculature. As in the case of the division of the right branch, the section of the left branch could be determined by the change of the contraction wave of the ventricles as seen by the eye. This was always confirmed later by the electrocardiograms.

The electrocardiograms following the division of the left branch were of uniform type and as characteristic as those that followed the cutting of the right branch (Fig. 5). The most prominent ventricular wave was upright in all leads, broad at the base and blunt and notched at the apex. The T-wave was a negative phase.

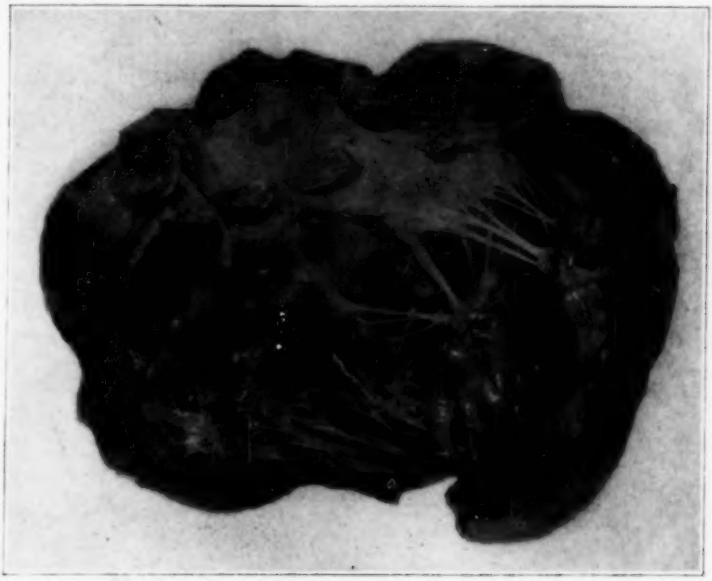

Fig. 6.—At the point marked X a small area of the endocardium was left intact.

The Division of the Subdivisions of the Left Branch of the Auriculoventricular Bundle.—The former experiments [1] covered fairly well lesions of the subdivisions of the left branch. The present observations were made to determine the extent to which the subdivisions could be divided and the electrocardiogram remain normal. We also wished to see whether we could bring back to normal the atypical electrocardiograms produced by cutting the smaller subdivisions of the left branch and dilating the left ventricle by the ligation of the coronary arteries.

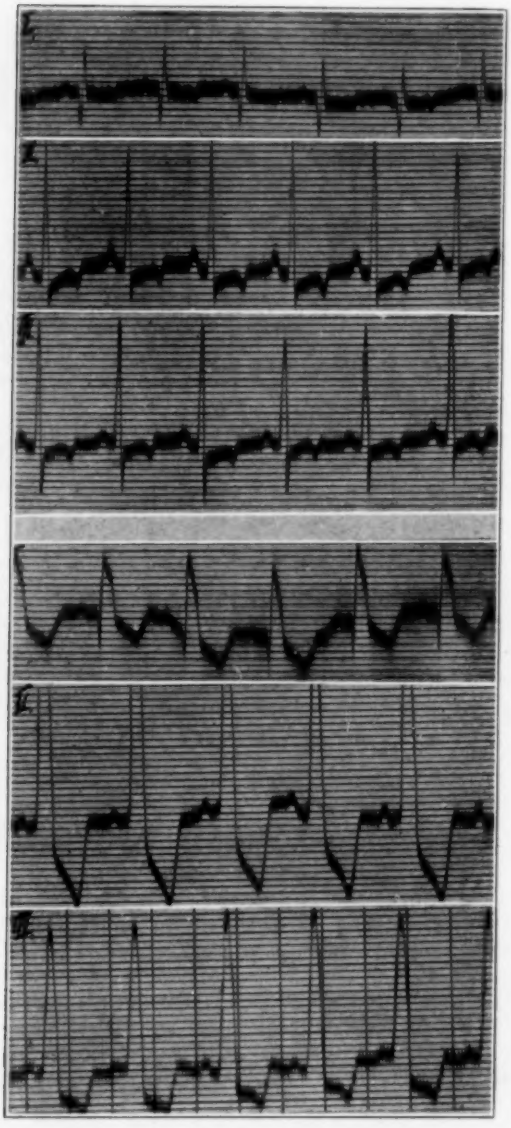

Fig. 7.—The upper figure is the initial electrocardiogram of the heart shown in Figure 6. The lower one was taken immediately after the incision was made in the endocardium.

In sixteen dogs, lesions of the subdivisions of the left branch were produced. The extent of the lesions varied from those involving the smaller ramifications to those involving two or more of the main subdivisions. In fourteen experiments, the incisions in the endocardium were very shallow and apparently did not disturb the muscular function of the heart. In two instances the incisions were more extensive than we anticipated. The heart soon dilated and the ventricles went into fibrillation.

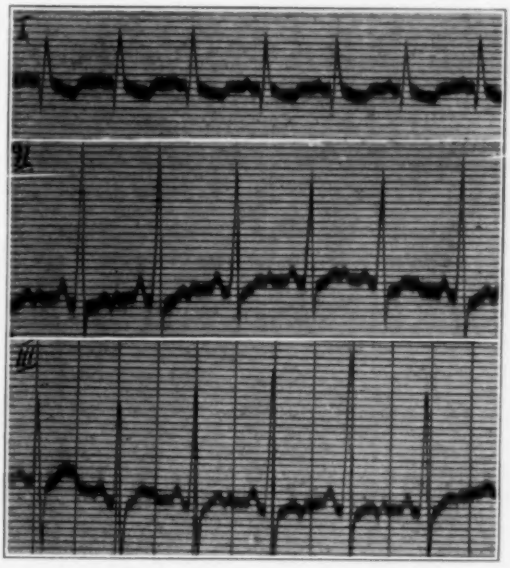

Fig. 8.—Electrocardiogram taken ten minutes following lower records in Figure 7.

The division of the smaller ramifications and of the larger subdivisions of the left branch produced no change in the Q R S group of the electrocardiogram. These results are in accord with those of my former work [1] and with those recently reported by Wilson and Herrmann.[4] The results in two experiments suggest the extent to which the main subdivisions can be divided and the electrocardiogram still remain normal. Immediately following the incision shown in Figure 6, the electrocardiogram was that of a complete branch block (Fig. 7). Within ten minutes the electrocardiogram returned to normal (Fig. 8).

4. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920.

It is to be noted that the incision is not continuous (Fig. 6). At the point marked X, a small area of endocardium was left intact. One possible explanation of the result is that one of the main subdivisions may have passed between the incisions, and thus was not cut but was merely rendered temporarily functionless by the trauma of the knife. In this way complete branch block resulted. It also occurred to us that blood might have entered the connective tissue sheath surrounding the cut subdivision and produced a transient block of the remaining undivided subdivisions. An electrocardiogram similar to the one shown in Figure 7 was obtained following the incision shown in Figure 9.

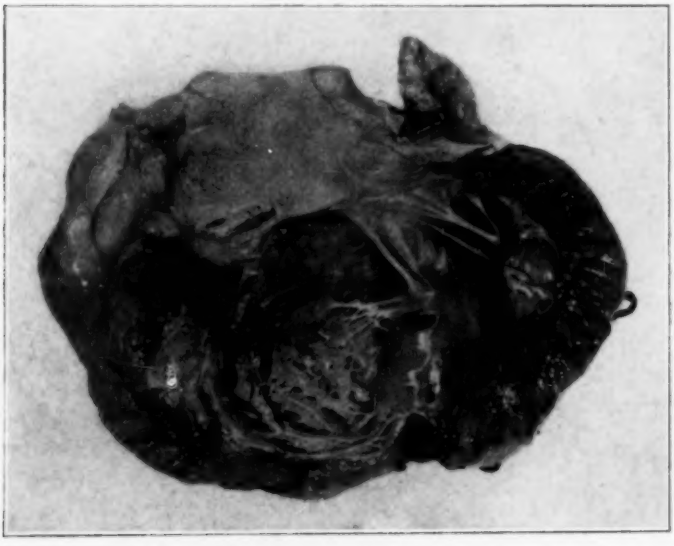

Fig. 9.—Following the incision there was a transient block of the left branch. There were at least two main divisions divided.

Here, again, the electrocardiogram returned to the normal in a few minutes. It would seem that at least two main subdivisions were divided by this incision.

Return to Normal of Aberrant Electrocardiograms.—In the work reported in 1920,[1] atypical electrocardiograms were produced by cutting subdivisions of the left branch and at the same time dilating the left ventricle by the ligation of branches of the left coronary arteries. No attempt was made in those experiments to bring these electrocardiograms back to normal. In the investigations here reported, we attempted to see if these results could be secured. In a measure, we were success-

ful. Figure 10 shows an abnormal electrocardiogram that was produced by the above method, which returned to the normal after the ligatures were removed from the coronary arteries. This change in the electrocardiogram was produced four different times in one experiment. Figure 11 shows the incisions that were made in the endocardium.

It was not always possible to bring the heart back after the ventricles had been dilated to such a degree that the contraction was atypical. Yet we were successful in four experiments. In twelve dogs, the ventricles began fibrillating as soon as the ligatures were removed from the coronary artery. In six of these, the electrocardiogram did not become atypical until just before the onset of the ventricular fibrillation. The Q R S group then resembled that of a premature ventricular contraction and the auricles were fibrillating.

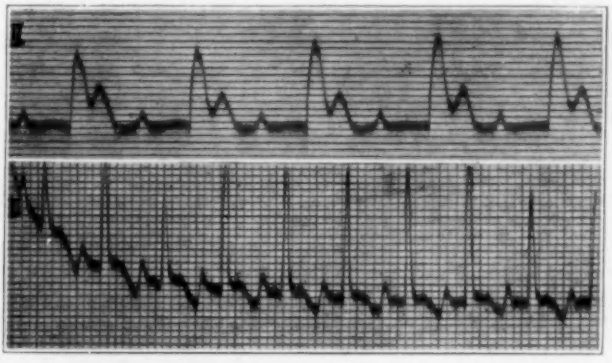

Fig. 10.—Top: Lead II. Atypical electrocardiogram produced by dilatation of the left ventricle by ligation of the branches of the left coronary arteries following the incision in the endocardium shown in Figure 11. Bottom: The electrocardiogram returned to normal after the ligatures were removed from the coronary arteries.

This type of curve was due either to a complete bundle branch block or regular recurring ectopic ventricular contractions. Some of the electrocardiograms of the former work were of this type.

COMMENT

The results obtained in these experiments following the division of the right and left branches of the auriculoventricular bundle are in accord with those obtained by Eppinger and Rothberger,[5] Lewis,[6] and

5. Eppinger, H., and Rothberger, J.: Ueber die Folgen der Durchschneidung des Tawaraschen Schenkel des Reizleitungs Systems, Ztschr. f. klin. Med. **70**:1, 1910.

6. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat. New York and London, 1920, p. 117.

more recently by Wilson and Herrmann, and quoted by Eppinger and Stoerck. In the dog the diaphasic ventricular complex of large amplitude and increased duration in Leads II and III with the T-wave an exaggerated positive phase is diagnostic of right branch block. The aberrant positive wave in all leads followed by a negative T deflection is equally characteristic of a block of the left branch.

The criteria used in the diagnosis of right and left bundle block in the dog do not always seem to hold in man. In those few instances in which a careful histological examination of the conduction system has been made, the findings have at times been at variance with those which are expected from the electrocardiogram. Eppinger and Stoerck verified the electrocardiographic diagnosis of right branch

Fig. 11.—Shows incisions in the endocardium lateral and mesial to the posterior papillary muscle.

block in two cases. Lewis [6] mentions one case in which the anticipated lesion was found at necropsy. Cohn and Lewis,[7] however, reported the histologic findings in four cases in which the electrocardiographic diagnoses were not substantiated. Oppenheimer and Pardee [8] recently had the opportunity of studying two patients in whom the lesions were found in the branch opposite to that expected from the electrocardiogram.

7. Cohn, A. E., and Lewis, T.: The Pathology of Bundle Branch Lesions of the Heart. Proc. New York Path. Soc. **14**:207, 1914.

8. Oppenheimer, B. S., and Pardee, H. E. B.: Site of the Cardiac Lesions in Two Instances of Intraventricular Heart Block. Read before the American Society of Clinical Investigation, Atlantic City, May 3, 1920.

The discrepancy between the anatomic and the electrocardiographic diagnosis may, in some instances, be due to the differences between the intraventricular conduction systems of man and the dog. This suggestion was offered by Oppenheimer and Pardee [5] in explanation of the findings in their two cases. This, however, should hold only for lesions of the left branch, for, according to Lewis, it is only the right branch that differs materially in man and the dog. The electrocardiogram of right branch block in man should correspond fairly well with that produced experimentally in the dog. This was true in the cases reported by Eppinger and Stoerck and in the one mentioned by Lewis.[6] It is to be remembered, too, that Cohn and Lewis,[7] in commenting on the findings in their four cases, pointed out that functional block of either of the branches may exist. If, however, we assume that the electrocardiograms of right branch block in man and of the block produced experimentally in the dog are similar, it is very difficult to explain the findings in one of the cases reported by Oppenheimer and Pardee.[5]

Lewis,[6] and Wilson and Herrmann [4] have called attention to the similarity of the preponderance curves and those of bundle branch block. Those individuals in whom aberrant electrocardiograms are found have had in the majority of instances gradually progressive degenerative changes in the myocardium sufficient to disturb the muscle balance in the ventricles. It would seem that a preponderance of the left ventricle would not particularly modify the electrocardiogram of a right branch block in that individual. This, at least, is shown by Lewis [6] by two curves from the same individual. The first was of right branch block. Later, the right branch functioned normally, and the electrocardiogram was that of left ventricular preponderance. The same might be expected of right ventricular preponderance and left branch block. When, however, the preponderance is on the same side as the branch block, one might expect that the electrocardiogram would be modified.

Lesions of the smaller subdivisions of the left intraventricular conduction system, even though they are extensive, do not necessarily change the form of the Q R S group. This was noted in the former work,[1] and is in accord with the results of Wilson and Herrmann.[4] In some instances, however, the electrocardiogram was changed to an atypical form by dilatation of the left ventricle caused by the ligation of branches of the left coronary artery. The fact that in four instances the curves returned to normal as soon as the ligatures were removed, and that this change in the form of the electrocardiogram was produced as many as four times in one of the experiments, would seem to indicate that functional changes in the myocardium may influence the transmission of the impulse within the ventricles.

The division of one or more of the main subdivisions also did not change the form of the Q R S group. It would seem from two of these experiments that the impulse may reach all parts of the left ventricle in normal time if one main branch is left intact. This is only possible through the free anatomic arborization between the main branches.

SUMMARY

Complete bundle branch block in the dog produces characteristic electrocardiograms that are diagnostic of the lesion. The division of the smaller subdivisions or even one or more of the main subdivisions did not change the form of the Q R S group. In some instances, however, these waves were changed to the atypical form after the cutting of subdivisions, by dilatation of the left ventricle, produced by ligating branches of the coronary arteries. This would indicate that functional change in the myocardium may influence the conduction of the impulse within the ventricles.

PRIMARY HEMANGIOLYMPHOMA OF THE HEMAL NODES: AN UNUSUAL VARIETY OF MALIGNANT TUMOR

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NEW YORK

In man and in certain of the lower vertebrates, nodal collections of lymphoid cells occur, and are divisible into two groups, namely, those which are provided with lymph sinuses, or ordinary lymph nodes, this group comprising by far the larger number; and those which are provided with blood sinuses, the latter being variously known as hemolymph nodes, splenolymph nodes, or more simply and better, perhaps, as hemal nodes. The exact anatomic position of the hemal nodes has not been determined. The preponderance of evidence, however, favors the view originally advanced by Vincent and Harrison,[1] that they are more closely related to the spleen, structurally and otherwise, than to the lymph nodes proper. In fact, Meyer,[2] in a series of injection experiments in sheep, has shown that the hemal nodes are in no way connected with the lymphatic system. Embryologically, the hemal nodes, like the spleen, are vascular bodies or masses of erectile tissue that have become modified in the process of development by the interposition of focal collections of lymphocytes in the meshes of a reticulum derived from the walls of blood vessels.[3]

In certain animals, notably in the bullock and sheep, hemal nodes are normally present and are conspicuous by their reddish color. In man, on the contrary, the hemal nodes in health, although present, are seldom, if ever, distinguishable by the naked eye, but in certain conditions of disease, particularly in anemias associated with changes in the spleen and bone marrow, and in syphilitic lesions of the spleen attended by overgrowth of connective tissue, they frequently come into view in the prevertebral fat tissues of the neck and thorax, and in the abdomen, more especially in the region of the promontory of the sacrum, as reddish or brownish red, rounded, oval or almond shaped bodies, varying in size from a few millimeters to 1 or 2 cm. Confirmatory evidence of their relationship to the spleen is furnished by Tizzoni [4] who, after experimental splenectomy in the dog, noted the occurrence of minute reddish nodules in the abdominal fat that he

1. Vincent and Harrison: J. Anat. & Physiol. **11**:176, 1897.
2. Meyer: Anat. Rec. **2**:62, 1908.
3. Sabin: Keibel & Mall's Human Embryology, **2**:750, 1912.
4. Tizzoni: Quoted by Mosler.

examined minutely and interpreted as collections of newly formed splenic tissue. Similar results have been obtained by Winogradow,[5] Warthin,[6] and others, the latter designating the bodies in question as hemolymph nodes, although recognizing their close structural resemblance to the spleen and their apparent similarity of function.

In certain lower forms of life, the spleen is a divided organ, and is more or less widely distributed through the abdomen, whereas in higher animals it usually occurs as a compact body. For example, in some of the invertebrate fish the spleen is strewn through the subserous tissues of the gastro-intestinal tract,[7] while in slightly higher forms it becomes separated and distributed in the tissues that run parallel with the stomach and intestine. In still higher fish, particularly among the selacians, the spleen consists of more or less completely separated nodules, a fact which tends to explain the occurrence of accessory spleens in man, in whom they are commonly encountered, from one or two to a dozen or more. In the case of an adult male, reported by Albrecht,[8] there was no evidence of a common spleen. On the contrary, splenunculi were scattered through the peritoneum to the extent of 400 or more. These splenunculi were highly vascularized, standing out as reddish or brownish red bodies which, at first glance, suggested the presence of a metastasizing tumor and, microscopically, were found to be plentifully supplied with lymphoid cells, the naked eye and histological appearances thus differing in no essential particular from the hemal nodes. Taking all things into consideration, it would seem that the hemal nodes represent an accessory system of diminutive spleens, whose prototype is to be found in the auxiliary system of lymph nodes occurring in man in the form of minute foci of lymphoid cells lying in the interstitial tissues of the thyroid, prostate, testicle, lungs, kidneys and adrenals, in the subcutaneous and submucous tissues and serous membranes, and elsewhere.[9] These deposits, like the hemal nodes in health, are small, and may escape detection in the routine histologic examination of tissues. Like the hemal nodes, again, they may be brought into prominence in disease, especially in conditions characterized by lymphoid hyperplasia, such as Hodgkin's disease, lymphosarcoma, pseudoleukemia, and in enteric fever.

As far as I have been able to learn, tumors in human beings springing from the hemal nodes have not hitherto been described. Of peculiar interest in this connection, however, is the observation of

5. Winogradow: Centralbl. f. d. med. Wissensch. **50**:900, 1882.
6. Warthin: J. M. Research, **2**:435, 1902.
7. Sobotta: Anatomie der Milz, Jena, 1914, p. 283.
8. Albrecht: Bietr. z. path. anat. u. z. allg. Path. **20**:513, 1896.
9. Symmers: Arch. Int. Med. **21**:237 (Feb.) 1918.

Mosler[10] who, in a dog, ten months after splenectomy, noted the occurrence of innumerable small, circumscribed, reddish nodules scattered through the omentum and mesentery, that closely resembled the structures identified by Tizzoni in animals similarly treated as newly formed masses of splenic tissue. In Mosler's animal the histologic examination was made by Roth, who interpreted the reddish bodies as neoplasmic formations and termed them hemorrhagic telangiectatic lymphomata.

In the pathological laboratories at Bellevue Hospital, I have had occasion to study two malignant tumors composed of groups of lymphoid cells associated with vast numbers of blood channels, the structure of the growths, as a whole, presenting a histologic picture that suggests derivation from the hemal nodes. One of the tumors was encountered as an accidental finding at necropsy in an adult male who had met death as a result of cyanid poisoning. The growth lay in the concavity of the left side of the pelvis and was about the size of an apple and reddish gray in color, while in the immediate vicinity and extending upward to the level of the first lumbar vertebra were a score or more of enlarged nodes of the same general description. The second case was that of a child, 3 years of age, and was marked by a huge collection of reddish tumor masses in the abdomen and by an extraordinary display of metastases distributed exclusively under the periosteum of various bones.

REPORT OF CASES

Case 1.—Nothing is known of the patient's clinical history. The body was subjected to necropsy in the pathological laboratories of Bellevue Hospital under the authority of the chief medical examiner of the City of New York, Dr. Charles Norris, to whom I am indebted for permission to present the findings.

Necropsy 7209.—The body was that of a well nourished man, 28 years of age. The general configuration was that of status lymphaticus. On section, a thymus weighing 20 gm. was found in the usual situation. On opening the abdomen, a tumor came into view lying in the concavity of the pelvis on the left side of the sacrum, reaching just to the brim of the pelvis. The mass measured 7 by 5 by 4 cm. and was rounded, deep reddish gray in color, homogeneous in apppearance and rather soft in consistence. On section, the growth presented a perfectly smooth, bluish red surface in which innumerable minute reddish specks could be seen alternating with faintly grayish areas. In the immediate vicinity of the tumor were ten or a dozen rounded or oval nodules, measuring from 2 to 3 cm. in diameter. On section, they presented essentially the same appearance as that of the larger growth. A chain of similarly enlarged lymph nodes extended upward on the left side of the aorta from the region of the pelvic growth to a point corresponding to the body of the first lumbar vertebra. These nodes were rounded or oval in outline, discrete, reddish gray in color and, on section, showed the same finely speckled appearance. The rest of the organs revealed no naked eye or histological changes worthy of note in the present connection.

Histologic Examination.—Sections were removed from the main tumor mass and from several of the enlarged lymph nodes in the vicinity, and were stained

10. Mosler: Deutsch. med. Wchnschr. **22**:337, 1884.

with hematoxylin and eosin and by the method of Van Gieson. Histologically, the growths were characterized by a great profusion of small, thin walled blood vessels, the lumina of which were distended by closely packed red blood corpuscles. Scattered between the vascular channels were diffuse collections of small round cells corresponding in all particulars to lymphoid cells as familiarly encountered. In other places rounded or oval lymphocytic foci occurred, the cells of which were rather loosely packed and arranged around small blood vessels whose walls, in many instances, were thickened and hyalinized, staining reddish by Van Gieson's method, the formation, as a whole, presenting a distinct resemblance to the malpighian bodies of the spleen. At the extreme

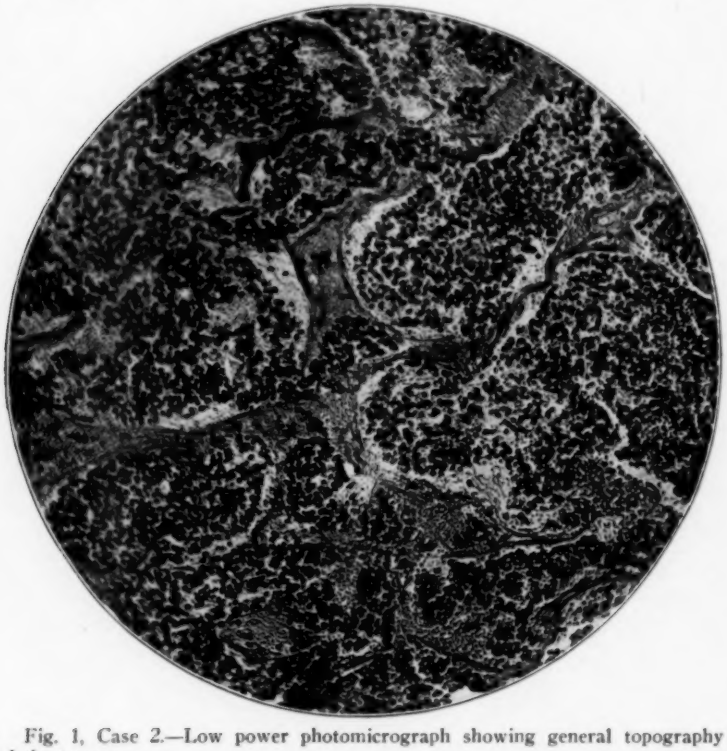

Fig. 1, Case 2.—Low power photomicrograph showing general topography of the tumor.

periphery, the tumor was limited by a rather thick connective tissue capsule which occasionally sent prolongations downward for a short distance, but, as a whole, trabeculation of the deeper parts of the growth was entirely missing and, in fact, with the exception of an occasional delicate strand of connective tissue, as revealed by Van Gieson's stain, no stroma was apparent, the lymphocytic cells being supported partly by reciprocal pressure and partly by the abundant network of small blood vessels around and between which they were distributed.

Case 2.—The patient, a female child, 3 years of age, was admitted to Bellevue Hospital May 5, and died four months later. It was not possible to obtain a satisfactory clinical history. The child is said to have felt indisposed for a

period of only three weeks before admission to the hospital, at which time small lumps appeared in the inguinal and femoral regions. The patient gradually became pale and weak and a tumor appeared above the right eye, the tissues in the immediate vicinity presenting a bluish discoloration. Physical examination showed an anemic poorly nourished child. Above and to the outer side of the right eye was a firm tumor, about the size of a small walnut. The skin covering the tumor and that of the corresponding eyelids was slightly discolored, and the veins above the growth were engorged. Over the posterior parietal and occipital regions were several other masses of the same consistence, but somewhat smaller in size. In the abdomen a large, irregular, firm growth was

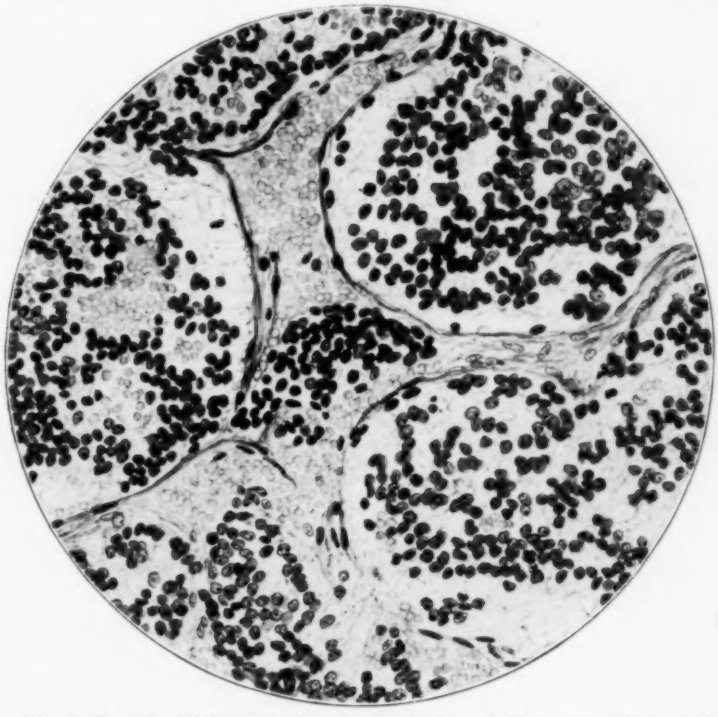

Fig. 2, Case 2.—High power drawing made from field corresponding to the center of the photomicrograph shown in Figure 1. The drawing illustrates the vascular channels lying in the supporting connective tissue, the presence of tumor cells in them, and free red corpuscles lying in the alveoli of tumor cells.

felt on the left side, extending from the level of the costal slope downward as far as the crest of the ilium and inward to the median line. White blood cells, 9,000; red cells, 1,500,000; hemoglobin, 30 per cent.

Necropsy 3766.—The body was that of a child, 3 years of age, weighing 27 pounds and measuring 97 cm. in length. The skin was pale. The arms and legs were thin, the abdomen prominent. The right upper eyelid was dark bluish in color; the lower eyelid faintly greenish. The conjunctivae were pale, but otherwise normal in appearance. On opening the abdomen, a small amount

of slightly blood tinged fluid was present in the pelvis and in the dependent portions of the peritoneal cavity. In the left hypochondrium was a massive tumor covered by peritoneum. The growth was globular in shape, measuring 10 x 9 x 6 cm. On section, it was found to be made up of a series of fused lymph nodes which were bright red in color. In the center of the mass was an area of liquefaction necrosis. The retroperitoneal lymph nodes were greatly enlarged and, on section, were bright reddish in color with alternating areas of whitish appearance and, together with the large globular tumor mentioned, weighed 650 gm. Enlarged lymph nodes of the same reddish color were present in the iliac region, in the anterior mediastinum, around the roots of the bronchi, and along the sides of the esophagus, some discrete, others fused. In the lower and external portion of the right frontal bone, near the orbit, was a tumor that measured 3 x 1 cm. On removing the scalp, which was edematous and somewhat thickened, it was found that the calvarium, as a whole, presented an irregularly mottled appearance, due to the presence of numbers of deep bluish foci, varying in size from ½ to 2 cm., corresponding to the distribution of tumor tissue beneath the periosteum. Large tumor nodules were revealed near the junction of the parietal and occipital bones, close to the sagittal suture, and a series of bluish foci, the whole measuring 4 or 5 cm. in length, was situated along the coronal suture near the longitudinal fissure. Near the posterior and median part of one of the parietal bones, was a mass that measured 2 by 2½ cm. and which, seen through the epicranium, presented a deep bluish color. On the external surface of the right occipital bone was still another bluish tumor mass which approximated 2 cm. in diameter. Over the whole extent of the inner surface of the calvarium and extending well down the sides of the vault of the cranium, the dura mater was dark bluish in color and the interval between it and the bone was extensively occupied by reddish, soft tumor tissue. On peeling the dura from the calvarium, some tumor tissue remained adherent to the bone and some to the dura. In places, the bone was superficially infiltrated, presenting a finely roughened appearance, as if punched out with small pins. There was a smaller amount of tumor tissue of the same character on the base of the skull, corresponding to the petrous portion of the right temporal bone and to the processes and body of the sphenoid and the clivus. The sternum in its middle portion anteriorly presented a bluish appearance which, on section, was found to correspond to reddish tumor tissue lying immediately under the periosteum. The inner surface of several of the ribs was finely speckled with bluish areas, pinpoint to pinhead in size, or slightly larger. In the lowermost ribs on both sides were large, deep bluish areas which, on section, corresponded to the presence of reddish tumor tissue lying between the periosteum and bone. In places, the surface of the rib appeared to be superficially infiltrated and softened by the growth. The largest bluish masses were found near the costal cartilages. Below the head of the right humerus there was a considerable sweep of infiltrating tumor tissue lying immediately under the periosteum. The lower half of the right femur showed large masses of tumor tissue beneath the periosteum, just above the right condyle. Where the tumor was most abundant, the cortex of the shaft was thinned and infiltrated. Section of the lower half of the right femur failed to show the presence of tumor tissue in the marrow. The periosteum of the anterior and left lateral surfaces of the sixth and seventh dorsal vertebrae was bluish in color and, on section, was found to be infiltrated by reddish tumor tissue which brought about superficial erosion of the bone. Section through the entire anterior half of the bodies of the vertebral column failed to show tumor tissue within the marrow. On removing the spinal cord, it was found that there were small areas of neoplasmic infiltration beneath one or two of the laminae and under the posterior surface of the body of one of the lower dorsal vertebrae.

The thymus was small, symmetrical in outline, and weighed approximately 10 gm. The gastro-intestinal tract, lungs, heart, liver, spleen, suprarenal

capsules, kidneys and other viscera showed no changes worthy of record in the present connection.

Histologic Examination.—Microscopic examination of sections removed from the primary growth in the abdomen showed the presence of great numbers of richly chromatic, rounded cells arranged in alveoli and surrounded by a highly vascularized connective tissue stroma. The tumor cells were rather loosely packed and the alveoli varied in shape and size. The individual tumor cells were somewhat larger than the ordinary lymphocyte and were provided with a rounded, fairly deeply chromatic, smooth or slightly granular nucleus, and very little cytoplasm. The connective tissue stroma was arranged in the form of delicate fibrils which frequently separated in such fashion as to surround sinuses of different shapes and sizes—some small and slitlike, others rounded, oval or angulated, practically all of them filled or distended by red cells. In many instances it was apparent that rupture had occurred, in which circumstances larger or smaller numbers of free red corpuscles were to be found strewn among the tumor cells or arranged in clumps. Massive hemorrhages were not uncommon. In many of the alveoli delicate, stringlike structures were to be seen insinuating themselves between the tumor cells or lying in definite bundles, representing, apparently, fibrin or some related substance. Areas of necrosis were numerous and often large. In one of the sections removed from the globular tumor in the abdomen, a few of the alveoli showed the presence of relatively huge, rounded or polygonal cells with abundant pale, finely granular cytoplasm and a centrally or somewhat eccentrically placed vesicular or fairly deeply staining nucleus. Cells of this type were encountered in the section in question to the number of only about twenty and, as a rule, they were caught in the meshes of the pinkish, thread-like masses of fibrin or fibrinoid material. Similar cells were not seen in any of the metastatic foci that were examined microscopically, and I am at a loss to account for them unless they represented tumor cells undergoing regressive changes, perhaps as a result of autolysis. Otherwise the microscopic examination of the metastatic deposits revealed an histology not to be distinguished from that of the original growth, that is to say, groups of lymphoid cells separated from one another by a stroma provided with blood sinuses.

CONCLUSIONS

1. There is a form of malignant tumor belonging to the lymphocytic group in which the naked eye and histological characteristics are such as to indicate derivation from the so-called hemal nodes, that is to say, the tumor arises in that locality where the hemal nodes are most frequently encountered, has a distinctive reddish or bluish red color and, microscopically, more or less faithfully counterfeits the histology of the hemal nodes in that it is composed of groups of lymphoid cells separated by innumerable distended blood sinuses with or without a supporting reticulum of connective tissue.

2. Two forms of neoplasmic growth are described in this paper—one occurring as a solitary mass without metastases, but attended by secondary nodules arising regionally, and hence to be classified as locally malignant; the other giving rise to multiple selective subperiosteal metastases, and hence highly malignant.

3. The variety of tumor described is apparently satisfactorily provided for under the appellation of malignant hemangiolymphoma or as hemangiolymphosarcoma.

4. Experience in the postmortem rooms of several hospitals has left me with the impression that primary tumors of the sort referred to in this paper occur with a fair degree of frequency. I do not refer to tumors of this type with multiple selective subperiosteal metastases—growths of this distribution, I assume, are pathologic curiosities—rather to tumors which present in a general way the ordinary characteristics of lymphosarcomata or malignant lymphomata, but which differ from them in that they are of a striking reddish or bluish red color. I have examined the only postmortem records at present available to me, namely, those of Bellevue Hospital, comprising some 7,000 protocols, but have not been able to find more than the two examples recorded in this paper. Once attention is directed to the existence of primary tumors of this sort, however, it should serve to attract observations from independent sources and thus to clarify our knowledge of the incidence and behavior of the highly vascularized neoplasms of the lymphocytic family.

5. The preponderance of evidence seems to favor the view originally advanced by Vincent and Harrison, that the hemal nodes are more closely related to the spleen, structurally and otherwise, than to the lymph nodes proper—that they represent a succession of diminutive spleens corresponding to the auxiliary lymphomatous deposits that normally exist in the interstitial tissues of many organs.

THE CHEMISTRY AND CLINICAL SIGNIFICANCE OF UROBILIN*

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Renewed interest in the physiology and clinical significance of urobilin has been aroused by the work of Wilbur and Addis [1] in this country, and by that of H. Fischer [2] and collaborators abroad. Clinical reports by Schneider,[4] Howard and Hansmann,[5] McCrudden,[6] Robertson,[7] Giffin, Stanford and Szlapka,[8] have served further to illustrate the practical value of urobilin determinations, in the bile, urine and feces.

In the present article, I wish briefly to review the present status of the urobilin question, and to tabulate the results of about 100 determinations on the urine and stool.

If we could determine accurately the daily excretion of bilirubin, it might aid in gaining an insight into this particular function of the liver and also afford a clue as to the extent of blood destruction, for at present it is generally believed that bilirubin is directly derived from hematin. Unless the patient or experimental animal has a biliary fistula, it is not possible to determine the bilirubin production, and even then we are assuming that the analytical methods at our disposal are sufficiently accurate to do so. If we attempt to estimate the bile pigments in the stool, we meet with at least two disturbing factors; the one is the difficulty of accurately separating the twenty-four hour amount of stool, and the other is the unknown factor of intestinal absorption and destruction. The errors arising from these uncertainties may be diminished somewhat by determining the average excretion for three or more days.

The normal stool, however, does not contain bilirubin itself, but instead two derivatives are found, which are closely related chemically, yet totally different in certain other respects. These substances are known as urobilin and urobilinogen respectively.

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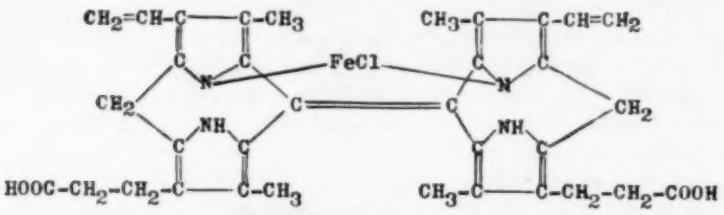
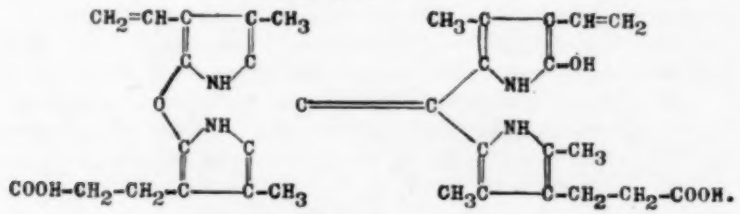
1. Wilbur, R. L., and Addis, T.: Arch. Int. Med. **13**:235 (Feb.) 1914.
2. Fischer, H.: Ztschr. f. Phys. Chem. **73**:204, 1911.
3. Fischer, H., and Meyer, P.: Ztschr. f. Phys. Chem. **75**:339, 1911.
4. Schneider, J. P.: Arch. Int. Med. **17**:32 (Jan.) 1916; J. A. M. A. **74**:1759 (June 26) 1920.
5. Hansmann, G. H., and Howard, C. P.: J. A. M. A. **73**:1262 (Oct. 25) 1919.
6. McCrudden, F. H.: Boston M. & S. J. **177**:907, 1917.
7. Robertson, O. H.: Arch. Int. Med. **16**:472 (Sept.) 1915; Arch. Int. Med. **16**:549 (Oct.) 1915.
8. Giffin, H. Z., Stanford, A. H., and Szlapka, T. L.: Am. J. M. Sc. **155**:562, 1918.

In 1868, Jaffe [9] described a reddish brown substance which he found in human and canine bile and which resembled one of the pathologic urine pigments. He found that both compounds absorbed certain rays between the *B* and *F* lines of the spectrum, and both exhibited fluorescence in the presence of zinc salts. The new pigment was called urobilin. It is remarkable that even at that early date, Jaffe was aware that the pigment resulted from the oxidation of a colorless chromogen which is now known as urobilinogen.

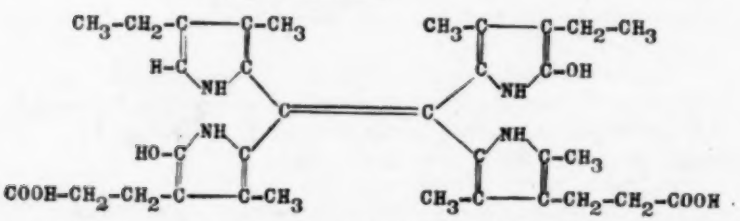
Hemin



Bilirubin



Urobilinogen



Urobilinogen has the formula $C_{33}H_{42}O_6N_4$. Fischer and Roëse [10] demonstrated that in common with hemin and bilirubin, it has four pyrole nuclei.

The formulas show that the three compounds are closely related, for in addition to the pyrole nuclei, each compound contains eight side

9. Jaffe, M.: Centralbl. f. d. med. Wissensch. 243, 1868; Centralbl. f. d. med. Wissensch. 177, 1869.

10. Fischer, H., and Roëse, H.: Ztschr. f. Phys. Chem. **89**:25, 1914.

chains which are almost identical in the three substances. Bilirubin may be regarded as an oxidized hemin while urobilinogen is a reduced bilirubin. This close chemical relationship cannot be ignored in a discussion of the derivation of the bile pigments; it is surely a weighty argument, favoring the view that bilirubin is directly derived from hematin.

Urobilinogen is a colorless crystalline compound which is quite soluble in many of the organic solvents. In the presence of oxygen or oxidizing substances, it is readily converted into urobilin. The close chemical relationship between bilirubin and urobilinogen is further illustrated by the ease with which the latter can be synthesized from the former substance. H. Fischer [3] was able to obtain urobilinogen in a 50 per cent. yield by reduction of bilirubin with sodium amalgam. He assumed that it was formed from one-half of the bilirubin molecule and accordingly named it hemibilirubin. Later he and Meyer-Betz [11] proved that urobilinogen (obtained from pathologic urine), and hemibilirubin were identical.

When urobilinogen is treated with Ehrlich's reagent, that is a solution of para dimethylaminobenzaldehyde in hydrochloric acid, a reddish condensation compound is formed which absorbs rays in the orange and green regions of the spectrum between the *D* and *E* lines. This red substance is strongly colored, one part of urobilinogen in 640,000 parts of water being sufficient to give the reaction,[3] and it is, therefore, well adapted for its determination. The reaction is not specific, for it may be obtained with any pyrole derivative that has a free hydrogen atom joined to one of the carbon atoms of the ring.

Urobilin is a reddish brown substance of uncertain composition. It is apparently a conglomerate of urobilinogen molecules that have been oxidized and polymerized. It is soluble in most of the organic solvents, is resinous in nature and exhibits fluorescence in the presence of zinc salts. It absorbs certain rays of the spectrum in the neighborhood of the *B* and *F* lines. With mercuric chlorid, it forms a reddish compound, the basis of the so-called Schmidt test. Urobilin can be reduced to urobilinogen in vitro by bacteria.

OCCURRENCE

Because urobilinogen and urobilin have the same clinical and physiologic significance, and for the sake of brevity, the term urobilin will be used to include both substances. Urobilin occurs in negligible quantities in the urine of normal people. Little definite information is available concerning its presence in the blood. We have attempted

11. Fischer, H., and Meyer-Betz, F.: Ztschr. f. Phys. Chem. **75**:232, 1911; Fischer, H., and Meyer-Betz, F.: Muench. med. Wchnschr. **59**:799, 1812.

to demonstrate it in the serums of patients who were excreting considerable quantities in the urine, but without success. When normal serum is heated with strong hydrochloric acid, it gives a positive Ehrlich reaction, but this may well be due to the liberation of tryptophane or its decomposition products. Some investigators claim to have found urobilin in the serum of pneumonia patients shortly before death. When it is added to blood, it disappears rapidly. Increased amounts of urobilin have been found in the stool and urine in diffuse hepatic lesions and in pernicious anemia and other conditions associated with a rapid and increased destruction of red blood cells. It is absent or almost absent from the stool in jaundice due to complete closure of the common bile duct and in severe diarrhoeas.

MECHANISM OF UROBILIN FORMATION

The voluminous literature dealing with this phase of the subject abounds in lengthy theoretical discussions and hypotheses. The so-called enterogenous theory had its chief exponent in Friedrich Mueller.[12] It appears to be least open to criticism and is best supported by experimental observations. In brief, it postulates that urobilin results from the reduction of bilirubin by the bacteria of the large intestine. The following evidence is submitted in support of the enterogenous theory: (1) The transformation of bilirubin into urobilin by bacteria in vitro. (2) The absence of urobilin in the stool in severe jaundice due to obstruction of the common bile duct. If, to such patients, bile be administered (by stomach tube) urobilin promptly appears in the stool. (3) Although bilirubin occurs in the stool of the new-born, urobilin is not present until the third day, when the bacterial flora of the intestine have had an opportunity to develop. (4) Diarrheal stools contain bilirubin but often no traces of urobilin. It is believed that increased peristalsis produces a rapid passage of bile through the intestine before the bacteria have had time to reduce bilirubin to urobilin.

Normally, some urobilin is absorbed from the intestine and brought to the liver where it is probably converted into bilirubin. If a large amount is absorbed, or if the liver is extensively diseased, then it may escape into the general circulation and be excreted by the kidneys. In pernicious anemia and hemolytic jaundice or as a result of the action of certain poisons, a large number of red cells are destroyed per unit of time, and the liberated hematin is changed into bilirubin, which, in turn, leads to an increased amount of urobilin in the stool. In recent years, hematin and bilirubin have been demonstrated in the blood serum in these pathologic conditions.

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12. Mueller, F.: Ztschr. f. klin. Med. **12**:45, 1887; Kongr. f. inn. Med. **11**:118, 1892.

The method which is now commonly used for determining urobilin is that of Wilbur and Addis.[1] A portion of the urine or fecal extract is treated with alcoholic zinc acetate solution and with Erlich's reagent. The mixture is then diluted until the spectral absorption bands of urobilin and the urobilinogen compound just disappear. The average normal excretion in the twenty-four hour stool, according to Wibur and Addis, is about 6,500 dilutions. In making the calculations for the stool, we purposely have omitted to consider the initial dilution due to admixture of reagents in order to make our results comparable with those of Wilbur and Addis.

CLINICAL SIGNIFICANCE

An increased amount of urobilin in the urine is frequently observed in diffuse lesions of the liver, as in fatty and parenchymatous degeneration, cirrhosis, diffuse neoplasm and quite constantly in the congestion of heart disease. Urobilinuria is found in the liver degeneration due to the acute infectious diseases, especially scarlet fever, rheumatism and lobar pneumonia.

When the flow of bile to the intestine is interrupted, the amount of urobilin in the stool is diminished, or it may be entirely absent, depending on the degree of obstruction of the bile duct. When bile or urobilinogen itself is administered to normal subjects, there is no increase of urobilin in the urine, but when administered to patients with liver disease, considerable quantities may appear therein.

In the various hepatopathies, we have usually found an increase in urobilin, either in the stool alone or in the urine alone, or in both.

An increased amount of urobilin in the stool is observed in cases of hemolytic jaundice and pernicious anemia, while in secondary anemia, a normal or subnormal excretion is the rule. Urobilin estimations afford a valuable means of differentiating the two conditions unless the liver itself is the seat of widespread pathologic change. Schneider[4] observed a marked increase of urobilin in the bile of pernicious anemia patients and his observations have been confirmed by investigators at the Mayo clinic.[5] We have examined the feces, the bile and the urine and have found the stool examination to be the most satisfactory. Attempts to demarcate the twenty-four hour amount of stool have been futile. We have observed large quantities of urobilin in the stool of pernicious anemia patients when microscopic examination of the blood showed no abnormality. Occasionally, the urobilin content of the stool decreases during the remission so frequently observed in this disease. While the method is far from accurate, especially in the hands of inexperienced workers, it is quite satisfactory for ordinary clinical purposes, if certain precautions are observed. It appears preferable

to determine the amount in the twenty-four hour stool, rather than that contained in a casual sample of bile; this also obviates the passage of the duodenal tube, a procedure which is often disagreeable to the patient.

One case is cited to illustrate the value of urobilin estimations as an aid in the differential diagnosis of primary anemia from secondary anemia.

An Italian, aged 51, entered the hospital in November, 1919, complaining chiefly of gastric distress and constipation which had lasted for two years, but which was never accompanied by real pain, vomiting or diarrhea. During the two weeks preceding admission, he had had a sudden attack of weakness and dizziness, followed by the appearance of tarry stools and shortness of breath. He had lost twenty-five pounds weight.

Physical Examination.—Evidences of neuroretinitis were noted in both eyes, occurring in an anemic man, measuring about 5½ feet and weighing 143 pounds. Roentgenologic examination of the alimentary canal and sigmoidoscopy was negative.

Laboratory Findings.—2,000,000 red blood cells; 40 per cent. hemoglobin; 6,800 white blood cells, of which 58 per cent. were polymorphonuclear. The blood smear showed irregularity in size and shape of the red cells, with central pallor and polychromatophilia on one occasion. The Wassermann test was negative. The gastric test meal contained no free hydrochloric acid, a total acidity of 32; no lactic acid and occult blood. The stool was repeatedly examined; it contained occult blood on one occasion only. It was never tarry. *The urobilin of the stool was persistently subnormal; there was none in the urine.*

The patient received two blood transfusions and was discharged after one month's stay in the hospital, with the diagnosis of pernicious anemia. This diagnosis was made largely because of the negative roentgen-ray findings.

Course.—During the following six months, the patient gradually gained fifteen pounds in weight. His blood now contained the normal number of red blood cells and 70 per cent. hemoglobin.

He was readmitted in June, 1920, because of the uncertainty of the diagnosis and because his gastric symptoms had increased in severity. The red blood cells now numbered 5,200,000, and the hemoglobin was 80 per cent. *The twenty-four hour quantity of stool contained only 1,760 dilutions of urobilin; the urine contained 400 dilutions on one occasion and 1,088 on another.*

Fluoroscopy now showed a mass in the region of the cardiac end of the stomach and this was confirmed by an exploratory laparotomy which further revealed metastic involvement of the liver and retroperitoneal lymph nodes.

In this case, the severe anemia during the earlier period of the disease was probably due to a profuse hemorrhage from the tumor. The low urobilin content of the stool was against pernicious anemia and in favor of a new growth. The late occurrence of urobilinuria was the result of involvement of the liver.

During the past two years, urobilin estimations of the urine and stool have been carried out on about 100 patients. The results are tabulated under three headings.

Table 1 is a record of figures obtained in a group of patients not suffering from pernicious anemia or straightforward liver disease. With few exceptions, the figures are within normal limits. Patient

44,545, though regarded as a case leukemia, was suffering from acute anemia at one time and during this period the urobilin in the stool was much increased. Patient 45,815 was suffering from sprue, a disease having several features in common with pernicious anemia, such as an anemia with a high hemoglobin index, sore tongue and achylia and the high urobilin excretion suggests an increased rate of blood destruction. Bahr [13] has encountered urobilinuria in several cases of sprue.

TABLE 1.—RESULTS OF EXAMINATION OF CASES OF MISCELLANEOUS DISEASES

History Number	Diagnosis	Red Blood Cells, Millions per Cmm.	Hemoglobin, per Cent.	Urobilin Dilution Units	
				Urine	Feces
43967	Viridans endocarditis	2.9	60	Trace	7200
44061	Malaria	3.6	50	Negative	8000
44067	Leukemia	1.6	48	Negative	1400
44200	Carcinoma pancreas	4.1	70	Negative	Trace (jaundice)
44198	Bronchopneumonia	3.9	70	Negative	4400
44322	Nephritis	2.9	75	Negative	8000
44545	Leukemia	2.2	29	2160	Trace, 18000 (blood crisis)
44387	Chronic bronchitis	5.6	70	Negative	6000, 7000
45175	Undiagnosed	4.7	78	Negative	6000
45233	Chronic nephritis	1.5	35	Negative	10000
45404	Carcinoma stomach	2.2	21	Trace	800
45297	Chronic cardiac disease	4.3	80	Negative	4800
46073	Dilatation of duodenum	5.2	85	Negative	6400
31655	Chronic colitis, dilatation of colon, phlebitis	4.5	85	Negative, 330	Trace, trace
45772	Perinephric abscess	4.3	74	Negative	4800
45815	Psilosis, hypertension	2.9	68	Negative	16000
44031	Carcinoma stomach, liver	2.5	35	Negative, 412, 1088	3200, 1760
46250	Purpura	1.8	22	590	20000
46612	Leukemia, acute myelog.	1.3	20	868	
46642	Chr. nephritis, arteriosclerosis	3.1	50	Negative	3200
47168	Splenic anemia	3.4	50	976, 858, 732	25000, 19000
46678	Splenic anemia	2.4	65	612, 288, 320	4000, 1632, trace
47306	Carcinoma stomach	2.5	30	200	4000
46538	Syphilis	3.5	35	.....	8000 (jaundice)
46170	Syphilis	5.2	80	Negative	3200
47815	Hypertension, syphilis	6.0	85	Negative	8000
48157	Chronic cardiac disease	5.1	90	Negative	3600, 12800
48753	Polycythemia	8.0	100	4160	
48321	Viridans endocarditis	3.3	55	Negative	6400
48420	Hodgkin's disease	4.2	75	Negative	2400
48092	Chronic nephritis	...	80	444	38400, 4800
48104	Hematuria	3.6	48	Negative	9600
48271	Ulcer of duodenum	1.8	28	Negative	8000
46638	Paroxysm, hemoglobinuria	4.4	70	Negative, trace	12800, 3200, 2720
31413	Purpura, streptococcus throat	5.6	75	432	4800
48631	Carcinoma peritonitis	4.3	44	340	3200
49381	Carcinoma peritonitis	4.8	55	Trace	6400

The increased urobilin excretion observed in patient 46,250, suffering from purpura, was probably due to the rapid disintegration of the extravasated red cells. In the case of splenic anemia (47,108), it is difficult to determine whether the high excretion was due to increased hemolysis or to involvement of the liver.

13. Bahr, P. H.: A Report on Researches in Sprue in Ceylon, 1912-1914.

TABLE 2.—Urobilin Excretion in Hepatic Diseases

History Number	Diagnosis	Red Blood Cells, Millions per Cmm.	Hemoglobin, per Cent.	Urobilin Dilution Units	
				Urine	Feces
42640	Cirrhosis	4.2	..	188	2400
41796	Cirrhosis, cholelithiasis	4.5	92	.....	1000 (jaundice)
45179	Cirrhosis	4.0	80	2400, 1360, 1200	23000, 16000
45247	Cirrhosis	5.5	80	1020	8000
45511	Cirrhosis	4.5	95	2536	3200
46114	Cirrhosis	4.0	70	1890	11400
47498	Cirrhosis	6.0	83	1740	16000
46895	Cirrhosis	4.1	..	Neg., Neg.	4000, 6400
46927	Cirrhosis	...	80	2000	16000
45434	Abscess	5.0	70	1740	
45367	Carcinoma	4.7	80	5200, 4760	4000
45855	Carcinoma	4.6	80	500, 376, trace	40000, 24000
47108	Carcinoma	...	..	1568, 1400	19800, 8000
45415	Carcinoma stomach, cirrhosis ?	5.1	65	564	3840
33081	Cholelithiasis	4.8	80	.....	16000
46983	Cholelithiasis	4.8	90	1320, 296	2400 (jaundice)
45496	Congestion	3.3	58	4120	
47283	Congestion	5.2	70	2576	2460
47135	Catarrhal jaundice during convalescence	...	..	.....	16000
44496	Catarrhal jaundice	3.2	70	Negative	2400
47171	Syphilis liver, spleen	4.6	42	1236, 2432	33000, 21120, 25000
45108	Carcinoma	...	..	320	16000
49499	Hodgkin's disease	4.2	..	3136	8000
32084	Cirrhosis	5.5	85	Negative	8000, 12800
48252	Syphilis liver	5.0	80	Negative	18000
48155	Carcinoma	5.8	90	672, 624, 756	16000
49045	Syphilis	4.3	80	1300	12800
48644	Cirrhosis	3.7	70	1600	21200
48921	"Salvarsan" jaundice	4.0	65	552	6400
48165	Catarrhal jaundice	5.0	110	1944	
48733	"Salvarsan" jaundice	5.0	75	Neg., Neg.	4800, trace
46170	"Salvarsan" jaundice	...	..	992, Neg., 600	800, 20000, 12800
30510	Jaundice, cholelithiasis	4.8	90	900	6400
48062	Carcinoma	4.2	90	1568	12800
49330	Jaundice (cause ?)	3.5	70	Negative	1600
47998	Tumor	6.8	80	.....	6400
49414	Splenomegaly, anemia	4.5	50	Trace	4000, 3200
49196	Congestion	4.4	70	1280	8000
48797	Syphilis	...	..	Negative	

TABLE 3.—Urobilin in Cases of Pernicious Anemia

History Number	Red Blood Cells, Millions per Cmm.	Hemoglobin, per Cent.	Urobilin Dilution Units	
			Urine	Feces
44321	2.2	70	.....	72000
44433	1.3	35	544	32000
44572	1.7, 1.5	35, 50	Trace, 1056	12000, 40000
44657	.....	.....	Negative, 1524	20000, 36000
40643	3.8	60	Negative	20000
44569	2.0	50	2200, negative	32000, 16000
45190	2.0	45	1120, 500	20000, 22000
45398	1.1	35	400, trace	18000, 12000
45506	1.4	50	2640	24000
45596	3.4	80	1520	21200
45067	3.0	58	608, 900	17760, 12800
37456	1.6	40	1044, 1118, 680	32000, 25600, 24000
46587	1.9	45	3000	20000, 16000
45773	1.0, 1.2	20, 25	1740, 7952, 1588	20000, 24000, 16000, 40000
47589	2.0	45	600	32000, 40000
47317	1.6	46	884	16000, 22000
48124	0.8	25	640, 200, 960	25000, 33260
45398	1.7	30	905, trace	100000, 40000
45559	0.8, 1.6	30, 40	Trace, negative	26400, 16000, 32000
46164	1.9	45	1944	40000
46498	2.0	40	672	40000
48640	1.2	38	1600	21200
48360	1.7	70	588, 800	16000, 24000
47780	0.8	30	1050, 1020	31800, 12000

Patient 48,092 was suffering from chronic nephritis of the retention type and secondary anemia. The high urobilin excretion was apparently due to the hemolytic activity of the retained waste products.

Patient 46,838, regarded as having paroxysmal hemoglobinuria, did not have an attack during the period of observation.

In the diseases of the liver, we have usually found an increase of urobilin in the urine alone or in the stool alone, or in both (Table 2).

In pernicious anemia, a high urobilin value was obtained in every instance if care was taken in the collection of the stool, and if the estimation was repeated sufficiently often (Table 3).

A STUDY OF THE S-T INTERVAL IN ONE THOUSAND AND TWENTY-EIGHT ELECTROCARDIOGRAMS

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The interval of the electrocardiogram from the termination of the S wave to the end of the T wave is being investigated by various observers in order to establish the method of its production and the significance of the variations from the normal. This interval is designated the S-T interval.

The present interpretation of the phenomena of the S-T interval rests, fundamentally, on the observations of a few workers. The foremost among these is Galvani [1] who, in 1786, discovered electric currents in the muscles of the frog. The flow of electric current from points of higher potential to points of lower potential was first observed by Nobili,[2] in 1824, shortly after his invention of the galvanometer. Kölliker and Müeller,[3] in 1855, while pursuing investigations similar to those of Galvani, found each beat of the frog's heart to be accompanied by a definite electric current. The next great advance was made by Waller,[4] in 1887, who succeeded in demonstrating the electric changes that accompany contraction of the cardiac muscle in intact animals and in man by the use of the capillary electrometer. During these investigations Waller was able to record the distribution in the remainder of the body of the electropotential which accompanies the beats of the human heart.

The final steps in the evolution of a means of graphically representing changes in electropotential during cardiac activity were made by Ader,[5] in 1897, and Einthoven,[6] in 1903. The invention of the string

1. Galvani, L.: The Encyclopedia Britannica. Ed. 11, Cambridge, Cambridge Univ. Press **11**:428, 1910.

2. Nobili, L.: The Encyclopedia Britannica. Ed. 11, Cambridge, Cambridge Univ. Press **19**:724, 1911.

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galvanometer by the former made the quantitative measurement of electropotential possible. The photographic apparatus added to Ader's instrument by Einthoven resulted in the electrocardiograph essentially as it exists today.

In attempts to reach a convincing explanation of the phenomena in the electrocardiogram which are graphically expressed in the interval extending from the termination of the S wave to the end of the T wave, various ideas have been presented. In a recent article Willius [7] reviewed the noteworthy contributions on this subject. His studies and investigations led him to believe that the horizontal portion, not infrequently absent, of the S-T interval represents an iso-electric state of the heart. The T wave, or the final portion of this interval, he believes to be the expression of preponderance of contraction on one side of the line of equipotential. Lewis,[8] however, does not believe that the problem has been definitely settled.

Variation in the length of the S-T interval has received slight consideration. Meakins [9] discussed his findings in a small number of cases. My own study consists of an analysis of 1,028 electrocardiograms, from 924 patients, made in the Mayo Clinic from Jan. 1, 1918, to June 1, 1918, and was undertaken in order to determine the frequency and associations of variations in the length of the S-T interval.

For clarity and brevity, the term "sinus rhythm" is used in the Mayo Clinic to designate all regular hearts with rates between 70 and 90 beats each minute; "sinus bradycardia" signifies all regular hearts with a rate below 70 beats each minute, while the term "sinus tachycardia" is used in all cases in which, with a regular heart, the rate is above 90 beats each minute, where the impulse originates in the normal pacemaker.

Normal S-T Interval.—The normal interval has been estimated at 0.28 second. Sixty-nine of the electrocardiograms (6.72 per cent.) recording sinus rhythm in normal hearts showed an average length of 0.28 second in all three derivations. Nine (13.04 per cent.) recorded prolonged S-T intervals, ranging from 0.29 to 0.34 second in any derivation, with an average for all derivations of 0.31 second. The shortest time interval for the S-T interval to be considered normal was 0.24 second. Two (2.89 per cent.) of the electrocardiograms recorded a shortened S-T interval. The average interval for all derivations in these two electrocardiograms was 0.20 second. Clinically, there was nothing to substantiate a diagnosis indicative of a cardiac

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lesion in the patients showing a prolonged or a shortened S-T interval, yet it is, perhaps, correct to suspect, because of its rarity in the normal heart and its frequency in the diseased heart, that it really speaks for some underlying, although yet undetermined, disturbance.

S-T Interval with Sinus Tachycardia.—In this group, 148 (14.39 per cent.) of the electrocardiograms were made from patients with normal rapid hearts. The average interval for all three derivations was 0.24 second. Six (4.05 per cent.) showed a prolongation of the interval ranging from 0.30 to 0.32 second in any derivation, or an average interval for all derivations of 0.31 second. The interval was found to be shortened in twenty-nine (19.59 per cent.). The interval ranged from 0.16 to 0.22 second in any derivation, with an average length for all derivations of 0.19 second.

Abnormal Hearts with Sinus Rhythm.—In this group were recorded 143 (13.91 per cent.) electrocardiograms from patients with intrinsic and extrinsic cardiac disease with normal cardiac rate. The average time for the S-T interval in all derivations was 0.30 second, or a slightly increased time interval for the whole series. Thirty-one (21.67 per cent.) showed a prolonged time interval. The average longest interval for any derivation was 0.36 second, and the average shortest was 0.30 second. In the patients with myocardial changes who showed prolonged intervals were associated: (1) myocardial degeneration with hypertension, nine patients, one with mild decompensation; (2) aortic regurgitation, four patients; (3) combined aortic and mitral valve regurgitation, one patient; (4) mitral regurgitation, four patients; (5) mitral stenosis, one patient; (6) combined mitral lesions, two patients; (7) general arteriosclerosis, six patients; (8) coronary sclerosis, three patients, and (9) dextrocardia, one patient. The rarity of shortened S-T interval in the moderately slow heart is evidenced by three (2.09 per cent.) electrocardiograms, which showed an average length of time for the S-T interval in all derivations of 0.21 second. The myocardial changes showing a shortened interval were associated in one case with aortic regurgitation, in one with arteriosclerosis, and in one with mitral regurgitation.

S-T Interval in Abnormal Heart with Sinus Tachycardia.—Under this heading 132 (12.84 per cent.) electrocardiograms were studied, and they showed an average time for the S-T interval in each derivation of 0.22 second. Rapid abnormal hearts as a group show a shortened S-T interval. The rarity of prolonged interval in the rapid abnormal heart was evidenced in four (3.03 per cent.) electrocardiograms in which the average longest interval for any derivation was 0.31 second. The clinical diagnosis in three of these cases was myocardial disease with arteriosclerosis, and in the fourth the diagnosis was aortic regurgitation. A shortened interval was found in twenty-nine (21.96 per

cent.) electrocardiograms; the longest interval for any derivation was 0.22 second, and the shortest was 0.16 second, with an average interval for all derivations of 0.18 second. The myocardial changes in the patients showing a shortened S-T interval in the electrocardiogram were associated with: (1) exophthalmic goiter, ten patients; (2) arteriosclerosis, ten patients; (3) mitral stenosis, one patient; (4) combined mitral lesions, two patients; (5) mitral regurgitation, two patients; and (6) congenital heart disease, four patients.

Premature Ventricular Contractions. — This phenomenon was observed in 143 (13.91 per cent.) electrocardiograms, in which the average S-T interval for each derivation was 0.28 second. Prolongation of the S-T interval in electrocardiograms showing premature ventricular contractions occurred in twelve (8.39 per cent.). The longest interval for any derivation was 0.40 second, and the shortest 0.30 second, with an average of 0.33 second for all derivations. A shortened interval with premature ventricular contractions was seen in three instances (1.39 per cent.). The average interval for all derivations was 0.20 second. The myocardial changes in the patients showing premature ventricular contractions in the electrocardiograms were associated with: (1) arteriosclerosis, fifty-seven patients; (2) myocardial degeneration and hypertension, three patients; (3) exophthalmic goiter, four patients; (4) auricular fibrillation, fourteen patients; (5) adenoma with hyperthyroidism, fifteen patients; (6) mitral stenosis, one patient; (7) mitral regurgitation, three patients; and (8) combined mitral lesion, one patient. In an undetermined group of forty-six patients with premature ventricular contractions no cardiovascular disease was found.

Premature Auricular Contractions.—Fifty-five (5.35 per cent.) electrocardiograms were studied in this group and showed an average length of time for the S-T interval in each derivation of 0.27 second. The S-T inerval was prolonged in eleven (20 per cent.) cases in this group; the longest interval for any derivation was 0.36 second, and the shortest interval for any derivation was 0.30 second, giving an average time for all derivations of 0.33 second. The association of premature auricular contraction with shortened S-T interval was observed in one electrocardiogram. The time interval was 0.20 second for all derivations. The myocardial changes in the cases presenting premature auricular contractions were associated with (1) adenoma with hyperthyroidism, five patients; (2) myocardial degeneration and hypertension, four patients; (3) arteriosclerosis, five patients; (4) mitral stenosis, one patient; (5) mitral regurgitation, two patients; (6) exophthalmic goiter, one patient; and (7) chorea, one patient. Premature auricular contractions were also found in an undetermined group of thirty-six cases.

Sinus Bradycardia in the Normal Heart.—A ventricular rate of less than 70 beats each minute was found in forty-eight (4.66 per cent.) electrocardiograms. The average time for the S-T interval for each derivation was 0.33 second. Slow hearts, as a group, show a prolonged S-T interval. In this series twenty-three (47.91 per cent.) electrocardiograms showed a prolonged interval; the greatest length of time for any derivation was 0.36 second, and the shortest 0.30 second, giving an average interval for all derivations of 0.32 second. In no instance was a shortened S-T interval found in the normal, unusually slow heart.

Sinus Bradycardia in the Abnormal Heart.—A ventricular rate of less than 70 beats each minute was found in fifty-five (5.35 per cent.) of the electrocardiograms from abnormal hearts. The average S-T interval for each derivation was 0.31 second. Forty (72.72 per cent.) electrocardiograms showed a prolonged S-T interval. The longest S-T interval in any derivation was 0.44 second, and the shortest 0.30 second, giving an average interval in all derivations of 0.36 second. A shortened interval did not occur in the slow, abnormal heart. The myocardial changes in the cases of sinus bradycardia showing a prolonged S-T interval were associated with: (1) myocardial degeneration and hypertension, five patients; (2) arteriosclerosis, nineteen patients; (3) coronary sclerosis, five patients; (4) mitral regurgitation, four patients; (5) mitral stenosis, one patient; (6) combined mitral lesion, two patients, and (7) aortitis, two patients. A patient with septic tonsils without heart involvement presented a prolonged S-T interval with an unusually slow heart. No cases of decompensation were recorded.

Sinus Arrhythmia in the Normal Heart.—This condition was found in twenty (1.9 per cent.) electrocardiograms. The average S-T interval for each derivation was 0.29 second. A prolonged S-T interval was observed in nine (45 per cent.) electrocardiograms. The longest interval for any derivation was 0.36 second, and the shortest 0.32 second. The average interval for all derivations was 0.34 second. A shortened interval was not observed.

Sinus Arrhythmia in the Abnormal Heart.—Fifteen (1.45 per cent.) electrocardiograms in this group showed an average S-T interval for each derivation of 0.28 second. A prolonged interval was found in eight (53.33 per cent.) electrocardiograms. The longest interval for any derivation was 0.36 second, and the shortest 0.32 second, giving an average interval for all derivations of 0.34 second. A shortened interval was found in two (13.33 per cent.) electrocardiograms. The S-T interval for all derivations was 0.22 second. The myocardial changes in the cases presenting a prolonged S-T interval were associated with: (1) aortic regurgitation, one patient; (2) coronary sclerosis, one

patient; (3) myocardial degeneration and hypertension, three patients; (4) arteriosclerosis, one patient; (5) congenital heart disease, one patient, and (6) mitral regurgitation, one patient. The myocardial changes in the group presenting a shortened S-T interval were associated with general arteriosclerosis, one patient, and attacks of paroxysmal tachycardia, one patient.

Auricular Fibrillation.—Eighty-one (7.88 per cent.) electrocardiograms were studied under this heading . The average S-T interval for all derivations was 0.22 second. A prolonged interval was observed in three instances (3.70 per cent.). The average time interval for all derivations was 0.33 second. A shortened interval was observed in thirty-three (40.74 per cent.) electrocardiograms. The longest

TABLE 1.—COMPARATIVE FREQUENCY OF PROLONGED S-T INTERVAL

Cases		Percentage prolonged
	Normal hearts	
23	Sinus bradycardia	47
9	Sinus rhythm	13
9	Sinus arrhythmia	4
6	Sinus tachycardia	4
	Abnormal hearts	
40	Sinus bradycardia	72
8	Sinus arrhythmia	53
2	Heart block	40
97	Left ventricular preponderance	22
31	Sinus rhythm	21
11	Auricular extrasystoles	20
22	Right ventricular preponderance	13
12	Ventricular extrasystoles	8
4	Aberrant Q R S Complexes	6
4	Sinus tachycardia	3
3	Auricular fibrillation	

interval for any derivation in this group was 0.22 second, and the shortest 0.12 second, giving an average for all derivations of 0.20 second. A group study of auricular fibrillation shows a shortened S-T interval.

Left Ventricular Preponderance.—This group, as well as that of right ventricular preponderance, is included in Tables 1 and 2 with the abnormal hearts, not because all the cases with preponderance were found associated with recognizable abnormal hearts, but for purposes of group study. Left ventricular preponderance was observed in 434 (42.21 per cent.) electrocardiograms. The average S-T interval for each derivation was 0.26 second. Ninety-seven (22.32 per cent) showed a prolonged interval; the longest time period for any derivation was 0.40 second, and the shortest 0.30 second, making an average

for all derivations of 0.30 second. A shortened interval was found in thirty-five (8.06 per cent.) electrocardiograms. The longest period for any derivation was 0.22 second, and the shortest 0.16 second, making an average for all derivations of 0.21 second.

Right Ventricular Preponderance.—One hundred sixty-six (16.05 per cent.) electrocardiograms were studied in this group. The average time interval for all derivations was 0.25 second. Twenty-two (13.33 per cent.) electrocardiograms showed a prolonged interval; the longest time for any derivation was 0.36 second, and the shortest 0.30 second, making an average for all derivations of 0.32 second. A shortened interval was found in thirty-three (20 per cent.) electrocardiograms. The longest interval for any derivation was 0.22 second, and the shortest 0.21 second.

TABLE 2.—Comparative Frequency of Shortened S-T Interval

Cases	Normal hearts	Percentage prolonged
29	Sinus tachycardia	19
2	Sinus rhythm	2
0	Sinus bradycardia	0
0	Sinus arrhythmia	0
	Abnormal hearts	
53	Auricular fibrillation	40
29	Sinus tachycardia	21
1	Partial heart block	20
12	Aberrant Q R S complexes	20
33	Right ventricular preponderance	19
2	Sinus arrhythmia	13
35	Left ventricular preponderance	8
3	Ventricular extrasystoles	2
3	Sinus rhythm	2
1	Auricular extrasystoles	0.9
0	Sinus bradycardia	0

Angina Pectoris.—Electrocardiograms were made from twenty-seven (2.62 per cent.) patients with angina pectoris. The cases with myocardial changes presented the following conditions: (1) general arteriosclerosis, seven patients; (2) cardiac hypertrophy with mitral regurgitation, three patients; (3) syphilitic aortitis, one patient; and (4) coronary sclerosis, nine patients. In a group of seven patients no cardiac lesion could be determined. The average time for the S-T interval for all the patients in all derivations was 0.26 second. Only three patients (11.11 per cent.) showed prolongation of the S-T interval with an average for all derivations of 0.32 second. Two (7.44 per cent.) patients showed a shortened S-T interval with an average for all derivations of 0.18 second. The systolic blood pressure

was increased in eighteen (66.66 per cent.), and the diastolic was above normal in twenty-one (77.77 per cent.). The findings in this group make it possible to state that there is no connection between the pain of this affection and variations in the length of the S-T interval. All the patients were subjected to a period of exercise after which a second electrocardiogram was made; this did not differ from the primary record.

Aberrant Q R S Complexes in all Derivations.—Sixty (5.83 per cent.) electrocardiograms in this group showed an average S-T interval for each derivation of 0.20 second. A prolonged interval was found in four (6.66 per cent.) electrocardiograms. The longest interval for any derivation was 0.40 second, and the shortest 0.32 second, making an average for all derivations of 0.36 second. In the twelve (20 per cent.) electrocardiograms with shortened interval the longest interval for any derivation was 0.20 second, and the shortest 0.16 second, making an average for all derivations of 0.19 second.

TABLE 3.—Age of Patients, in Decades, Manifesting Change in S-T Interval

Decades	Patients With Prolonged S-T Interval	Patients With Shortened S-T Interval
0 to 10	0	9
11 to 20	10	9
21 to 30	27	37
31 to 40	64	37
41 to 50	62	43
51 to 60	64	31
61 to 70	50	17
71 to 80	9	2

Partial or Complete Heart Block.—There were five patients in this group which showed an average S-T interval for each derivation of 0.27 second. Of these patients two (40 per cent.) showed an average interval for all derivations of 0.32 second, while one electrocardiogram showed an interval of 0.21 second in Derivation I, 0.24 second in Derivation II, and 0.20 second in Derivation III.

Sex and Age.—The 287 (27.91 per cent.) electrocardiograms which showed a prolonged S-T interval were made from 175 (60.97 per cent.) males, and 112 (39.03 per cent.) females. One hundred eighty-five (17.99 per cent.) electrocardiograms which showed shortening of the S-T interval were made from seventy-four (40 per cent.) males, and 111 (60 per cent.) females. The higher percentage of females in the group showing shortened S-T interval is due to the greater frequency of exophthalmic goiter in females.

Blood Pressure.—A study was made of each group of the systolic and diastolic blood pressures in order to determine if there was any relation between variations in blood pressure and the length of the

S-T interval. The unimportance of blood pressure in variations in the length of the S-T interval is shown in Table 4.

T Wave Negativity.—This phenomenon was observed in 511 (49.70 per cent.) electrocardiograms in various combinations and in various derivations. It is interesting to note that, as in the studies of Willius, T wave negativity was never found in Derivation II alone or in combined Derivations I and III. The S-T interval was found prolonged in Derivation I with T wave negativity in six patients, and in forty-two (8 per cent.) patients in Derivation III. In combination the S-T interval was found prolonged in association with T wave negativity once in Derivations I and II, twice in Derivations I, II and III, and three times in Derivations II and III. The S-T interval was shortened in Derivation I three times in association with T wave

TABLE 4.—Relation of Blood Pressure to S-T Interval

	Normal Hearts		Abnormal Hearts		Normal Hearts				Abnormal Hearts			
					Prolonged S-T Interval		Shortened S-T Interval		Prolonged S-T Interval		Shortened S-T Interval	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Sinus rhythm	128	79	148	77	133	80	130	76	140	80	163	49
Sinus tachycardia	140	73	132	68	151	85	153	86	134	85	141	65
Sinus bradycardia	123	72	135	78	127	77	...	..	146	77	...	..
Sinus arrhythmia	113	73	128	73	117	70	...	..	135	72	125	81
Auricular fibrillation	...	..	114	63	...	..	...	..	133	63	130	79
Left ventricular preponderance	...	..	145	81	...	..	...	..	144	84	140	75
Right ventricular preponderance	...	..	126	74	...	..	...	..	132	78	197	116
Angina pectoris	...	..	151	88	...	..	...	..	148	103	160	80
Aberrant Q R S complex	...	..	152	86	...	..	...	..	147	86	162	75

negativity, and twenty-two (4 per cent.) times in Derivation III. The interval was found shortened with T wave negativity in combined Derivations I and II, six times; in Derivations I, II, and III, six times, and in Derivations II and III, six times.

Exophthalmic Goiter.—Electrocardiograms were made from eighty-one (7.87 per cent.) patients. Forty-two (51.85 per cent.) electrocardiograms showed a normal S-T interval, three (3.71 per cent.) a prolonged interval, thirty-three (40.61 per cent) a shortened period, and in three (3.71 per cent.) the interval could not be read because of auricular fibrillation in which the irregularity was such as to obscure the definition of the T wave. The frequency of shortened S-T interval in exophthalmic goiter is sharply contrasted with the infrequency of this finding in cases of adenoma with hyperthyroidism. In the latter condition, the S-T interval was shortened six times (16.21 per cent.) in patients with auricular fibrillation, once in a patient with simple

sinus tachycardia; it was prolonged in six (16.21 per cent.) patients. Thirty-seven (3.59 per cent.) electrocardiograms were made from patients with adenomas with hyperthyroidism.

DISCUSSION

Variations in the length of the S-T interval are common. Of the 1,028 electrocardiograms studied a total of 472 (44 per cent.) showed an abnormal length of the interval. Prolongation (27 per cent.) is more frequently observed than shortening (18 per cent.). The comparative frequency of changes in the length of the interval is shown in Tables 1 and 2. The data presented demonstrate the lack of a constant relationship of variation in the length of the interval with any other phenomena in the electrocardiogram. It is to be noted, however, that prolongation is found more often in slow hearts, while shortening is found more often in the rapid heart. There is an intimate relationship between cardiac rate and length of the S-T interval.

The pathologic conditions associated with variations in the length of the S-T interval are diverse. A study of the clinical diagnosis clearly shows that there is no organic lesion of the cardiac structures which is constantly associated with a variation in the length of the S-T interval. A prolonged interval is found in electrocardiograms made from hearts, which, although diseased from an anatomic standpoint, are usually capable of functioning properly. The reverse holds for the shortened interval which is associated with cardiac lesions which have eventuated into more or less marked cardiac distress. Shortening, nevertheless, is not always found in hearts that are functionally embarrassed.

It might be suspected that interference with the conduction apparatus would have a constant bearing on the length of the S-T interval. This does not hold true. There are no constant changes in cases of partial or complete block. Lesions affecting the interventricular ramifications of the conduction bundle, which present themselves as aberrant Q R S complexes, are also not associated with distinctive variations in the length of the S-T interval. This deduction is based on the forty-four (74 per cent.) electrocardiograms of this type which showed no variation in the length of the S-T interval. Partial or complete heart block and aberrant Q R S complexes are the expression of involvement of the conduction apparatus before branching and very shortly after branching, so that it can be definitely stated that lesions of the conduction system have no distinctive influence in variations in the length of the S-T interval.

It is safe to believe that no anatomic condition of the heart can cause, per se, variation in the length of the S-T interval. This belief, which is borne out by the data of this study, must be correct if the

theory of electric potential is correct. If the horizontal portion of the S-T interval is the expression of an iso-electric state, and if the T wave is the expression of preponderance of contraction on one side of the line of equipotential, it follows that only some factor which either accelerates or retards the rate of change in electropotential can cause a variation in the length of the S-T interval. This factor is not brought out by my investigations. It is, no doubt, electrochemic in nature rather than histopathologic. This assumption is suggested by the electrochemic theory of living matter recently advanced by Crile.

CONCLUSIONS

1. The normal time period of the S-T interval ranges from 0.24 second to 0.28 second.

2. Variations in the length of the S-T interval are common.

3. Variations are independent of anatomic lesions.

4. The length of the S-T interval is more dependent on cardiac rate than any other factor.

5. Variations in the length of the S-T interval are not a constant accompaniment of any of the other phenomena of the electrocardiograms.

6. Males present variations in the length of the S-T interval slightly more often than females.

7. Variations in the length of the S-T interval are suggestive of retardation or acceleration of the rate of change in electropotential.

PERFORATION OF THE INTERVENTRICULAR SEPTUM OF THE HEART

WITH REPORT OF A CASE*

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Perforation of the interventricular septum of the heart, aside from cases of congenital malformation, in the great majority of cases is due either to rupture of an interventricular aneurysm or to ulcerative endocarditis. Perforation from other causes, such as rupture of a hydatid cyst,[1] has been described but such cases are relatively very rare.

CARDIAC ANEURYSMS

Cardiac aneurysms have long been the subject of reports in the literature, and many excellent monographs have been written on the subject. It is said to have been first described by Guzman Galeati in 1757.[2] Also Thurman[3] reports a case from the manuscripts of John Hunter described in 1757. The first monograph was written by Breschet in 1827.[4] Pelvet,[5] in 1867, gave an excellent discussion of the subject. Bourland,[6] in 1904, without giving references, reports having collected 147 cases from the literature. Osler and McCrae[7] refer to 135 cases, and Friedlander and Isaacs[8] reported a case recently.

Aneurysms of the heart may form in the valves, walls or interventricular septum. They may be acute or chronic. Acute aneurysms are associated with acute endocarditis and will be considered under the discussion of that condition. Chronic aneurysms are, in the great majority of cases, the result of chronic myocarditis and fibrosis. As a rule, the chronic myocarditis is due to arteriosclerosis of the coronaries, and the anterior branch is the one most commonly affected. The left ventricular wall, near the apex, is the most usual site, as would logically follow as the result of the anterior coronary being most often affected. The aneurysmal formation may vary from the slightest aneurysmal

*From the Medical Service Massachusetts General Hospital.

1. Crowther, B.: Austral. M. J. **2**:362, 1880.
2. Cited by Pelvet.
3. Cited by Pelvet.
4. Cited by Pelvet.
5. Pelvet: Des Aneurysmes du Coeur, Paris. Delchage, 1867.
6. Bourland: Aneurysm of the Heart, Am. J. M. Sc. **128**:323, 1904.
7. Osler and McCrae: Modern Medicine, Ed. 2, Philadelphia, W. B. Saunders Company, **4**:482, 1915.
8. Friedlander, A, and Isaacs, R.: Interventricular Cardiac Aneursym with Heart Block, J. A. M. A. **75**:1778 (Dec. 25) 1920.

dilatation to a definite aneurysmal sac. The wall is thinned and the muscle tissue is largely replaced by fibrous tissue. There frequently are adhesions to the pericardium and rupture is fairly common.

Aneurysms of the interventricular septum differ in no essential respect from cardiac aneurysms in general, except as to location. According to Klein [9] they were not described until 1839. In contradistinction to cardiac aneurysms in general, they are most commonly found at the base of the heart, in the "undefended space" or pars membranacea. As the whole septum derives its blood supply from the anterior coronary artery which is most commonly involved in cardiac aneurysms, some additional reason has been sought for the occurrence of septal aneurysms at the base in the large majority of cases. Klein mentions gross abnormalities and increased pressure in the left ventricle, due to hyperthophy, acting on the weakest part of the wall. Others have discussed the character of the tissue forming this part of the septum which is fibrous in character. Also endocarditis is more frequent in this region due to easy extension from the valves, causing the formation of a weak spot and a subsequent aneurysm.

PERFORATION OF THE INTERVENTRICULAR SEPTUM

Perforation of the interventricular septum due to ulcerative endocarditis has also been reported fairly frequently. Callender [10] reported a case in 1858, while Fournier,[11] in 1884, discussed the condition at length and reported a case of his own and seven others which he collected. Gennari,[12] in 1904, reported a case and gave a short bibliography.

For reasons which are similar to those given for the more frequent occurrence of septum aneurysms in the pars membranacea, perforation due to ulcerative endocarditis is also most likely to occur in that area. Proximity to the valves from which involvement often occurs by direct extension, the character of the tissue, the poor blood supply in that area, congenital defects, all make this area peculiarly susceptible to such an infection with resultant perforation.

The symptoms of perforation of the interventricular septum are indefinite and are not pathognomonic of the condition. In the cases of perforation of fair size, occurring acutely, there is the picture of sudden cardiac failure. When, as in the majority of cases, it occurs more

9. Klein, G.: Zur Aetiologie der Aneurysmen der pars membranacea septi Ventriculorum Cordis and deren Ruptur; Arch. f. path. Anat. **118**:57, 1889.

10. Callender: Med. Times & Gaz. Feb. 1858.

11. Fournier, H. C.: Etude sur les Perforations de la Cloison interventriculaire dans l'Endocardite Ulcereuse, Paris, 1884, Davy.

12. Gennari, C.: Sopra un Caso di perforazione del setto interventriculaire determinata de endocardite ulcerosa. Riv. Crit. di clin. med. **5**:717, 1904.

gradually, there is only a greater or smaller increase in the signs of cardiac distress which the patient already shows. The murmurs are not characteristic. Fournier speaks of cyanosis as an important sign but in Talamon's [13] case there was no cyanosis. Gennari says that the most important signs are pulsation to the right of the sternum, dilatation of the right ventricle, a murmur to the right of the sternum transmitted to the right and a thrill in the same area.

While cardiac aneurysms are fairly common, aneurysms of the interventricular septum are rather rare and perforation of the septum due to their rupture is even more rare. Including cases of perforation of the septum due to ulcerative endocarditis, a careful search of the literature since 1879 has yielded but twenty-two cases of perforation of the septum due to all causes, which were reported as such. Peacock [14] in 1854, reported a case in which the rupture also included the ventricular wall. Reinhardt, [15] in 1857, reported a case due to rupture of an aneurysm of the interventricular septum; Talamon cited a case in 1878; V. Buhl [16] has reported five cases and Klein and Lee [17] each one. Callender apparently reported the first case of perforation due to ulcerative endocarditis in 1858. Fournier, in 1884, reported one case of his own and seven others. Peron,[18] Fisher [19] and Gennari have each reported one case. In all of these cases the perforation occurred at the base of the septum and in none of them was there found a perforation similar to the one occurring in the case to be described below, in which case the perforation occurred near the tip of the septum a short distance above the apex.

REPORT OF CASE

History.—R. B. (East Medical 238,660), a widowed, white woman, aged 52, entered the Massachusetts General Hospital Sept. 13, 1920. She was born in Pennsylvania and had lived in Massachusetts forty-seven years. Her family, marital and social histories were essentially negative. According to her past history, her general health had been good until about ten years previously.

13. Talamon, C.: Endocardite du Septum et Aneurysme interventriculaire; perforation de la Cloison; endocardite de l'infundibulum; Progrès méd. **7**:984. 1878.

14. Peacock: Tr. Path. Soc. Lond. **5**:102, 1854.

15. Reinhardt: Zur Anatome und Pathololgie der dünnen Stelle in der Herzcheidewand; Arch. f. path. anat. **12**:129, 1857.

16. Buhl: Ztschr. f. Biol. 253, 1880.

17. Lee, A. E.: Case of ruptured aneurysm in the Ventricular Septum with Sudden Death; U. S. Naval Bull. **2**:49, 1908.

18. Peron, A.: Endocardite droit infféctieuse post peurperil; perforation de la Cloison interventriculaire per une lesion unique ayant Amene une insufficiance tricuspidienne et insuffisiance aortique; Bull. Soc. Anat. de Par. **70**:198, 1895.

19. Fisher, H.: A case of Ulcerative Endocaritis involving the Pulmonary Valve, causing a perforation of the ventricular septum, gangrene of the nose and ears and multiple infarcts of the kidneys; Proc. Path. Soc. Phila. **6**:98, 1902.

Since then she had had frequent tonsillitis. She had entered this hospital on three previous occasions. The first time (East Surgical 204,937), in the fall of 1915, she complained of several attacks of epigastric pain, nausea, vomiting, headache, clay colored stools, dysuria, and frequency of urination. Operation showed only a slightly inflamed appendix which was removed. Her second entry a year later (East Surgical 210,450), was for a similar complaint plus backache and a vaginal discharge. At this time the urine showed sugar on two of five examinations and albumin three times. At her third entry, two years later (East Surgical 282,282), she complained of the same right upper quadrant pain plus moderate dyspnea on exertion and nocturia. Physical examination showed the heart not enlarged and slight sinus arrhythmia. The urine showed 2.0, 0, and 2.9 per cent. sugar, respecively, on three examinations. Following her discharge she was treated in the diabetic clinic of the outpatient department for about a year. She was placed on a restricted diet and did well, her urine on the last day she attended the clinic showing only the slightest possible trace of sugar.

On her present admission she stated that she had had slight dyspnea with mild anginoid pains, and slight palpitation when tired or excited, occasional orthopnea and edema for eight or ten years, and a dry, unproductive cough for years. She had been on a general diet since she had left the outpatient department eighteen months previously.

Present Illness.—The present illness occurred suddenly, ten days before admission, with substernal distress during moderate exertion, which had passed off in about twenty minutes. That evening, while in bed, she had a sudden, sharp, substernal pain, radiating to the back, shoulders and left arm. It was associated with dypsnea and orthopnea and lasted for twenty-four hours. It has recurred several times since then. For six days she has had increasing edema of the feet. Vomiting occurred three days before entrance, at first associated with the anginal pains. For three or four days her cough has grown worse but there has been no sputum.

Physical Examination.—On admission the following positive findings were noted: Obesity and slight cyanosis of the mucous menbranes. Lungs: Showed slight dulness at both bases posteriorly, with fine moist râles. Heart: Apex impulse was neither seen nor felt. The sounds were regular and rapid (140). There was a thrill at the apex and a blowing murmur over the whole precordium both of which seemed diastolic in time but it was impossible to determine the time accurately because of the rapid heart rate. The murmur was loudest to the left of the sternum, in the fourth and fifth interspaces and was transmitted to the axilla and the back. A very soft systolic murmur was heard at the apex. The pulses were equal, synchronous and of normal volume and tension. The arterial walls were not palpable and the brachials were not tortuous. The blood pressure was 125 systolic and 80 diastolic.

The leukocyte count was 14,000; hemoglobin, 80 per cent., and the smear and differential count were normal. The nonprotein nitrogen was 47.1 mg. per 100 c.c. of blood. The blood Wassermann was negative.

Treatment and Course.—The following day the urine showed 7.1 per cent. sugar. Carbohydrate was fed in the form of sugar water and she received an ampoule of digifolin intravenously. The note of that day says: "Cyanosis, pallor, blowing murmur at the fourth chondral space probably systolic, second sound not heard, rate rapid. Small amount of pleural fluid. History suggests coronary disease."

On the second day the carbon dioxid tension of the alveolar air was 17. The leukocyte count was 20,000. On the third day the apex rate was 180-190 with a high pulse deficit, apparently auricular fibrillation. The murmur over the precordium was definitely systolic and the sounds were faint. The electrocardiogram taken a short time after this examination showed simply a sino-auricular tachycardia, with a somewhat inverted T wave. One hour

later, the rate was 120 and perfectly regular. Paroxysms of aurcilar fibrillation were thought quite likely. The respirations were from 35 to 45 per minute. The digitalis was increased. The urine showed 2.17 per cent. sugar and a positive diacetic acid test. The blood sugar was 0.54 per cent. The following day her condition was much worse and she was practically unconscious. She was given orange juice and fat free milk and 400 c.c. of a 5 per cent. sodium bicarbonate solution intravenously. Acetone bodies in the blood were 3.72 mg. per 100 c.c. The patient grew rapidly worse and died that evening, the fourth day after admission.

Necropsy.—Necropsy 4,116, twelve and one half hours postmortem (abstract). The body is that of a white woman, 52 years of age, 162½ cm. long, well developed and stout. Head: Not examined. Trunk: Slight edema of the feet and ankles. Skin and Mucous Membranes: Pale. On section, subcutaneous fat in large amounts. Abdomen and contents essentially negative. Diaphragm: Negative. Pleurae: Right, a few adhesions to the pericardium and a few posteriorly. Left, a few adhesions posteriorly and one to the diaphragm. Trachea and Bronchi: Contain a moderate amount of reddish brown, frothy fluid. The mucoso is brownish red. Lungs: The tissue is slightly leathery, salmon colored and yields a considerable amount of thin, brownish red, frothy fluid. Pericardium: Negative. Heart: The heart weighs 310 gm.; a little enlarged. The myocardium, except in an area to be described, is of fairly good consistency, pale, brown red. The right ventricular wall is three to four mm. thick; the left ten. The columnae are fairly well marked on the right but flattened on the left. The right cavity is slightly dilated. The left ventricle, anterio-laterally to the right and opposite to the interventricular septum in its lower half, presents a pouch like dilatation 8x4½x2½ cm. The cavity on this side was otherwise negative. The auricular appendages are negative. Valve circumferences—mitral 10 cm., aortic 6 cm., tricuspid, 12 cm., pulmonic 8 cm. The aortic cusps show a slight amount of sclerosis. The valves are otherwise negative. Foramen ovale closed. Right coronary artery free, fairly capacious and shows only a slight amount of fibrous sclerosis. Left, first portion clear and shows only a very small amount of fibrous sclerosis but at a point about 3½ cm. from its origin the left descending branch is practically occluded by a fibrous plaque. The vessel and its branches beyond this point are very small and dwindle away in the wall of the dilatation previously mentioned. The myocardium in the region of the dilatation is about 3 mm. thick and shows a leathery fibrosis. At a point at the base of the dilatation, in the region of the interventricular septum, a few cm. above the apical region there is a perforation of the septum about 6x3 mm. The margins are a little irregular, somewhat rounded and the tissue is perhaps a little softer here than elsewhere. On the endocardium of the left ventricle in the region of the dilatation there is a thin, greyish-yellow, weakly adherent layer of thrombotic material. On the right ventricular side of the opening, arising from its margins, there is a rather weakly adherent, frank columnar, thrombotic mass about 2½x2x1½ cm. The mass presents a rather thick, greyish-yellow, granular outer shell with a mottled surface. It surrounds a dirty, brownish to blackish, red, softer material. Aorta: The first portion, just above the cusps, shows a small area of arteriosclerosis; elsewhere it is fairly smooth. The ascending and descending portions show a small amount of fibrous sclerosis. The abdominal portion shows a moderate amount of fibrous sclerosis with several thin, small, calcareous plates. The great branches are negative. Pulmonary artery, Veins and Venae Cavae: Negative. Liver: Negative. Gall bladder: Contains about twelve minute, blackish-green concretions. Pancreas: Shows general, well marked, fatty infiltration. The pancreatic tissue presents as small, pale, scattered islands in the ocean of fat tissue. Spleen and suprarenals: Negative. Kidneys: Negative aside from some injection of the vessels. Pelvis, Ureters and Bladder: Negative.

Microscopic Examination. — Pancreas: Fat present. Islands few and far between. The islands show some hyaline degeneration of their cells. Kidneys: Acute degeneration. Liver: Moderate fatty metamorphosis of the liver cells.

Bacteriologic Report.—Culture of heart's blood on plain agar "Good growth of streptococci."

Anatomic Diagnosis.—Diabetes Mellitus; slight arteriosclerosis; arteriosclerotic occlusion of the left anterior coronary artery with an area of chronic interstitial myocarditis and degeneration and perforation of the interventricular septum; mural thrombi of the ventricles; slight hypertrophy and dilatation of the heart; septicemia (streptococcus).

SUMMARY

A case is reported presenting an interesting example of perforation of the interventricular septum of the heart in an unusual location; the heart was normal except for a limited area of sclerosis. The patient also showed slight general arteriosclerosis and diabetes mellitus.